Aus der Klinik für Radiologie und Nuklearmedizin
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Über die Weiterentwicklung der interventionellen Onkologie: von der Technik bis zur Patientenselektion.

Habilitationsschrift

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Inhaltsverzeichnis

1. Vorwort, Liste der Publikationen

Die hier vorliegende Habilitationsschrift bezieht sich auf die im Folgenden genannten Veröffentlichungen in chronologischer Reihenfolge.
Damit wird den Ausführungsbestimmungen zur Habilitationsordnung der Otto-von-Guericke-Universität Magdeburg in der Fassung vom 26.04.2016 für eine kumulative Habilitationsschrift entsprochen.

Veröffentlichung 1

Hepatic toxicity after radioembolization of the liver using (90)Y-microspheres: sequential lobar versus whole liver approach.
Seidensticker R, Seidensticker M, **Damm R**, Mohnike K, Schütte K, Malfertheiner P, Van Buskirk M, Pech M, Amthauer H, Ricke J.
Cardiovasc Intervent Radiol. 2012 Oct;35(5):1109-18.

Veröffentlichung 2

Interventional radiological procedures in the therapy for colorectal liver metastases.
Damm R, Seidensticker R, Ricke J, Seidensticker M.
Zentralbl Chir. 2013 Feb;138(1):76-83.

Veröffentlichung 3

Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization.
Garlipp B, de Baere T, **Damm R**, Irmscher R, van Buskirk M, Stübs P, Deschamps F, Meyer F, Seidensticker R, Mohnike K, Pech M, Amthauer H, Lippert H, Ricke J, Seidensticker M.
Hepatology. 2014 May;59(5):1864-73.

Veröffentlichung 4

Safety of repeated radioembolizations in patients with advanced primary and secondary liver tumors and progressive disease after first selective internal radiotherapy.
Zarva A, Mohnike K, **Damm R**, Ruf J, Seidensticker R, Ulrich G, Seidensticker M, Pech M, Ricke J, Amthauer H. J Nucl Med. 2014 Mar;55(3):360-6.

Veröffentlichung 5

Prospective randomized trial of enoxaparin, pentoxifylline and ursodeoxycholic acid for prevention of radiation-induced liver toxicity.

Seidensticker M, Seidensticker R, **Damm R**, Mohnike K, Pech M, Sangro B, Hass P, Wust P, Kropf S, Gademann G, Ricke J.

PLoS One. 2014 Nov 13;9(11):e112731.

Veröffentlichung 6

Radioablation of liver malignancies with interstitial high-dose-rate brachytherapy : Complications and risk factors.

Mohnike K, Wolf S, **Damm R**, Seidensticker M, Seidensticker R, Fischbach F, Peters N, Hass P, Gademann G, Pech M, Ricke J.

Strahlenther Onkol. 2016 May;192(5):288-96.

Veröffentlichung 7

Y90 Radioembolization in chemo-refractory metastastic, liver dominant colorectal cancer patients: outcome assessment applying a predictive scoring system.

Damm R, Seidensticker R, Ulrich G, Breier L, Steffen IG, Seidensticker M, Garlipp B, Mohnike K, Pech M, Amthauer H, Ricke J.

BMC Cancer. 2016 Jul 20;16:509.

Veröffentlichung 8

Cytokines and 90Y-Radioembolization: Relation to Liver Function and Overall Survival.

Seidensticker M, Powerski M, Seidensticker R, **Damm R**, Mohnike K, Garlipp B, Klopffleisch M, Amthauer H, Ricke J, Pech M.

Cardiovasc Intervent Radiol. 2017 Aug;40(8):1185-1195.

Veröffentlichung 9

Percutaneous radiofrequency ablation in the treatment of pulmonary malignancies: efficacy, safety and predictive factors.

Streitparth T, Schumacher D, **Damm R**, Friebe B, Mohnike K, Kosiek O, Pech M, Ricke J, Streitparth F.

Oncotarget. 2018 Jan 18;9(14):11722-11733.

Veröffentlichung 10

Image-guided Interstitial Brachytherapy in the Management of Metastasized Anal Squamous Cell Carcinoma.

Heinze C, Omari J, Othmer M, Hass P, Seidensticker M, **Damm R**, Ricke J, Pech M, Powerski MJ.

Anticancer Res. 2018 Sep;38(9):5401-5407. doi: 10.21873/anticanres.12870.

Veröffentlichung 11

Local ablation or radioembolization of colorectal cancer metastases: comorbidities or older age do not affect overall survival.

Seidensticker R*, **Damm R***°, Enge J, Seidensticker M, Mohnike K, Pech M, Hass P, Amthauer H, Ricke J.

BMC Cancer. 2018 Sep 10;18(1):882. doi: 10.1186/s12885-018-4784-9.

*** geteilte Erstautorenschaft , ° korrespondierender Autor**

Veröffentlichung 12

Ultrasound-assisted catheter placement in CT-guided HDR brachytherapy for the local ablation of abdominal malignancies: Initial experience.

Damm R, El-Sanosy S, Omari J, Damm R, Hass P, Pech M, Powerski M.

Rofo. 2018 Oct 11. doi: 10.1055/a-0636-4055.

Veröffentlichung 13

Biliary duct stenosis after image-guided high-dose-rate interstitial brachytherapy of central and hilar liver tumors : A systematic analysis of 102 cases.

Powerski M, Penzlin S, Hass P, Seidensticker R, Mohnike K, **Damm R**, Steffen I, Pech M, Gademann G, Ricke J, Seidensticker M.

Strahlenther Onkol. 2018 Nov 23. doi: 10.1007/s00066-018-1404-1.

Veröffentlichung 14

Image-guided interstitial high-dose-rate brachytherapy in the treatment of metastatic esophageal squamous cell carcinoma.

Omari J, Heinze C, Wilck A, Hass P, Seidensticker M, **Damm R**, Fischbach K, Ricke J, Pech M, Powerski M.

J Contemp Brachytherapy. 2018 Oct;10(5):439-445. doi: 10.5114/jcb.2018.79230.

Veröffentlichung 15

Radioablation by Image-Guided (HDR) Brachytherapy and Transarterial Chemoembolization in Hepatocellular Carcinoma: A Randomized Phase II Trial.
Mohnike K, Steffen IG, Seidensticker M, Hass P, **Damm R**, Peters N, Seidensticker R, Schütte K, Arend J, Bornschein J, Streitparth T, Wybranski C, Wieners G, Stübs P, Malfertheiner P, Pech M, Ricke J.
Cardiovasc Intervent Radiol. 2018 Nov 28. doi: 10.1007/s00270-018-2127-5.

Veröffentlichung 16

Needle track seeding in hepatocellular carcinoma after local ablation by high-dose-rate brachytherapy: a retrospective study of 588 catheter placements.
Damm R, Zörkler I, Rogits B, Hass P, Omari J, Powerski M, Kropf S, Mohnike K, Pech M, Ricke J, Seidensticker M.
J Contemp Brachytherapy. 2018; 10(6):1-6. doi: 10.5114/jcb.2018.80626

Veröffentlichung 17

Small renal carcinoma: the “when” and “how” of operation, active surveillance, and ablation
Wendler JJ, Liehr UB, **Damm R**, , Powerski M, Brunner T, Schostak M, Pech M
Pol J Radiol 2018; 83: e595-e603. doi: 10.5114/pjr.2018.81282

Veröffentlichung 18

Radioablation of Hepatic Metastases from Renal Cell Carcinoma With Image-guided Interstitial Brachytherapy.
Omari J, Heinze C, **Damm R**, Hass P, Janitzky A, Wendler JJ, Seidensticker M, Ricke J, Powerski MJ, Pech M.
Anticancer Res. 2019 May;39(5):2501-2508. doi: 10.21873/anticanres.13370.

Veröffentlichung 19

First report on extended distance between tumor lesion and adjacent organs at risk using interventionally applied balloon catheters: a simple procedure to optimize clinical target volume covering effective isodose in interstitial high-dose-rate brachytherapy of liver malignomas.

Hass P, Steffen IG, Powerski M, Mohnike K, Seidensticker M, Meyer F, Brunner T, **Damm R**, Willich C, Walke M, Karagiannis E, Omari J, Ricke J.

J Contemp Brachytherapy. 2019 Apr;11(2):152-161. doi: 10.5114/jcb.2019.84798. Epub 2019 Apr 29.

Veröffentlichung 20

Prospective evaluation of CT-guided HDR brachytherapy as a local-ablative treatment for renal masses: a single-arm pilot trial.

Damm R, Streitparth T, Hass P, Seidensticker M, Heinze C, Powerski M, Wendler JJ, Liehr UB, Mohnike K, Pech M, Ricke J

Strahlenther Onkol. 2019 Jul 25, doi: 10.1007/s00066-019-01501-1

2. Einleitung

2.1 Lokale und lokoregionäre Therapien in der Onkologie

Neben der systemischen, chirurgischen und strahlentherapeutischen Therapie hat sich in den letzten zwei Jahrzehnten zunehmend ein weiterer Behandlungszweig für solide Tumorerkrankungen etabliert: die interventionelle Onkologie als Teilbereich der Radiologie [1]. Während die Behandlung primärer Karzinomerkrankungen zunächst auf das hepatozelluläre und cholangiozelluläre Karzinom beschränkt war, findet man zunehmend auch einen hohen Stellenwert in der Behandlung bei Primärtumoren der Nieren und Lunge. Ein Großteil der Eingriffe erfolgt jedoch für die Therapie von metastasierten Erkrankungen [2].

Der Hauptschwerpunkt findet sich hierbei in der Behandlung des hepatisch metastasierten, kolorektalen Karzinoms (**Veröffentlichung 2**).

Die interventionellen Techniken lassen sich in die lokal-ablativen Verfahren wie die Radiofrequenz- und Mikrowellenablation (RFA/MWA) sowie die interstitielle Brachytherapie (iBT) einerseits und die transarteriell-lokoregionären Verfahren wie die transarterielle Chemoembolisation (TACE) und Y90-Radioembolisation (Y90-RE) andererseits gliedern. Sie basieren auf unterschiedlichen physikalischen Prinzipien und haben eine vollständige (Ablation) oder partielle (Zytoreduktion) Tumorausschaltung zum Ziel [3].

Bei den lokal-ablativen Verfahren erfolgt der Zugang zum Zielorgan perkutan mit speziellen Nadeln und Applikatoren unter Zuhilfenahme einer Bildführung mittels Sonographie, Computertomographie oder Magnetresonanztomographie. Die Behandlung erfolgt direkt im Tumor unter Generierung von Hitze zur Erzeugung einer Koagulationsnekrose (RFA/MWA) bzw. durch Radioablation infolge einer einzeitigen Hochdosisbestrahlung (iBT). Demgegenüber wird ein transarterieller Zugang über die Leistenschlagader für die loko-regionären Verfahren verwendet, um über Kathetersysteme unter angiographischer Führung aktiv beladene Partikel in das Gefäßbett von Lebertumoren einzubringen (TACE, Y90-RE).

Aufgrund der geringen Invasivität können die meisten Verfahren in den typischen Anwendungsgebieten auf eine Allgemeinanästhesie verzichten und werden unter einer Lokalanästhesie mit begleitender Analgosedierung durchgeführt (**Veröffentlichung 2,6,9,11**).

Eine Ausnahme hiervon stellt lediglich die auf der Membranwirkung elektrischer Felder beruhende irreversible Elektroporation dar, die aufgrund von Muskelkontraktionen bei der perkutanen Ablation in Allgemeinanästhesie durchgeführt werden muss [4,5].

Die Indikationsstellung zu den verschiedenen, interventionellen Verfahren beruht im Wesentlichen auf zwei Faktoren:

(i) Technische Durchführbarkeit der Verfahren in Bezug auf Zugangsweg, Komplikationen und Organfunktion bei einer hinreichenden Effektivität,

(ii) Klinisch-onkologische Sinnhaftigkeit einer lokalen bzw. lokoregionären Behandlung bei einer meist metastasierten Grunderkrankung.

Wie die interventionellen Therapien dies erfüllen können, stellen das **Kapitel 3** für die technischen Aspekte (i) und das **Kapitel 4** für den klinischen Kontext (ii) vor.
Einen Überblick über die einzelnen Verfahren, deren Effektivität und Komplikationen sowie deren klinischen Einsatz gibt der **Anhang** in den Tabellen 1 - 6.

Ein weiteres, jedoch selteneres Betätigungsfeld der interventionellen Radiologie stellt neben der ablativen und zytoreduktiven Therapie der Tumorerkrankung selbst das Management von tumorbedingten Komplikationen dar, welches hier nur erwähnt sein soll und im Wesentlichen nicht Gegenstand dieser Arbeit ist [6].

In den folgenden Kapiteln der Einleitung folgt eine kurze Einordnung der wissenschaftlichen Erkenntnisse zur Tumorbiologie und Metastasierung sowie onkologischer Therapieprinzipien im Kontext der interventionellen Radiologie.

2.2 Oligometastasierung und Tumorbiologie

In Anlehnung an die chirurgische Therapie bei metastasierten Tumoren verfolgen die lokalen Ablationstechniken (Radiofrequenzablation, Mikrowellenablation, interstitielle Brachytherapie) zunächst das Ziel, alle sichtbaren Tumorlokalisationen vollständig zu behandeln bzw. alle sichtbaren Tumorzellen vollständig abzutöten (**Veröffentlichung 2**). Ein wichtiger Begriff ist in diesem Zusammenhang die Oligometastasierung, denn eine systemisch disseminierte Metastasierung kann technisch durch lokale Verfahren nicht kontrolliert werden und muss gleichsam systemisch medikamentös behandelt werden. Eine genaue Definition in Hinblick auf Größe, Anzahl und Verteilung an Metastasen liegt für den Begriff der Oligometastasierung nicht vor, meist geht man jedoch von höchstens 5 Metastasen in 2 bis 3 Organen aus, wie dies beispielsweise in der europäischen Leitlinie zur Behandlung des metastasierten, kolorektalen Karzinoms erwähnt ist [7]. Andere Arbeiten gehen von maximal 3 Metastasen in 2 Organen aus [8]. Eine wichtige Rolle in der Indikationsstellung zur lokalen Therapie – sei dies eine chirurgische Resektion oder interventionelle Ablation – hat die Vorhersage, ob eine zum Entscheidungszeitpunkt oligometastasierte Tumorerkrankung auch im Verlauf dieses biologische Wachstumsverhalten zeigen wird. Gerade bei der Erstvorstellung einer metastasierten Erkrankung kann klinisch der folgende Krankheitsverlauf nicht sicher vorhergesagt werden. Entgegen der ursprünglichen Annahme kann ein offensichtlich lokal begrenzter Metastasierungsphänotyp durch bisher undetektierte Mikrometastasen in eine polymetastatische Tumorerkrankung fortschreiten oder polymetastatische Klone unter den Tumorzellen werden unter einer Therapie selektiert und zeigen eine vermehrte Proliferation [9]. Diese beiden tumorbiologischen Hypothesen müssen für die Ermöglichung einer besseren Patientenselektion entsprechend durch Vorhersagemodelle bzw. Biomarker genauer aufgeklärt werden. Zum einen kann anhand des bekannten Metastasierungsphänotyps (Metastasenanzahl, Größendifferenzen und Zeitintervalle) durch die Anwendung von Wachstumsmodellen eine Prädiktion der zur erwarteten Tumorbiologie getroffen werden [10]. Zum anderen gibt es Bestrebungen, den oligo- bzw. polymetastatischen Genotyp hinter dem sichtbaren Phänotyp auf Basis von microRNA-Profilen genauer zu charakterisieren und damit der dringenden Nachfrage nach Biomarkern für eine bessere Patientenselektion zu genügen [11,12].

Die wichtigste klinische Evidenz zur lokalen Therapie bei Oligometastasierung stellen die Ergebnisse der CLOCC-Studie dar [13,14]. In dieser randomisierten Studie wurden 119 Patienten mit metastasiertem kolorektalen Karzinom (mCRC) mit ≤ 10 irresektablen Metastasen in die Gruppen Chemotherapie (Folinsäure,5-Fluorouracil,Oxaliplatin ± Bevacizumab) allein vs. Chemotherapie plus Radiofrequenzablation randomisiert. Für den Fall, dass die systemische Chemotherapie eine Konversion zur Operabilität erreichte, wurde zusätzlich die chirurgische Therapie zugelassen und die interventionelle Strategie folglich als „aggressive Lokaltherapie“ bezeichnet. In der ersten Veröffentlichung 2012 wurde in beiden Gruppen ein gutes Gesamtüberleben für Chemotherapie allein mit 40,5 Monaten sowie Chemotherapie plus Lokaltherapie mit 45,3 Monaten erreicht - das Ergebnis war jedoch nicht statistisch signifikant (p=0,22) [13]. Erst die Langzeitergebnisse aus der Analyse im Jahr 2017 mit einem Nachsorgezeitraum von 9,7 Jahren zeigten aufgrund der geringeren Anzahl zensierter Patienten einen statistisch signifikanten Überlebensvorteil (p=0,01) nach Chemotherapie plus Lokaltherapie gegenüber Chemotherapie allein [14].
Ein wichtiger Aspekt für die klinische Einordnung der CLOCC-Studie ist der Verlauf der Überlebenskurven in der Kaplan-Meier-Analyse: eine sichtbare Auftrennung im Verlauf beider Gruppen tritt nach etwa 3 Jahren ein. Dieser Zeitraum entspricht dem typischen Überleben nach systemischer Therapie des mCRC mit einer Kombinationschemotherapie aus Oxaliplatin bzw. Irinotecan mit 5-Fluorouracil und Folinsäure sowie einer eGFR/VEGF-Antikörpertherapie mit Bevacizumab, Cetuximab oder Panitumumab (mediane Überleben in diversen Patientenkollektiven im Bereich 25 bis 41 Monate) [15-17]. Da auch eine kurzfristig zur Polymetastasierung fortschreitende Erkrankung mit einer systemischen Therapie zunächst zu kontrollieren ist, scheinen offensichtlich nur die wirklich oligometastasierten Patienten von der aggressiven Lokaltherapie langfristig zu profitieren, während die Patienten mit kürzerem Überleben in mutmaßlich beiden Gruppen frühzeitig polymetastasierende Fälle darstellen. Dies unterstreicht den Bedarf an vorhersagekräftigen Wachstumsmodellen und Biomarkern, deren Anwendung in Zukunft bei der Patientenselektion noch bessere Ergebnisse der lokalablativen Therapie erwarten lässt.

2.3 Zytoreduktion und Ansprechtiefe

Auch für den Fall, dass eine vollständige, lokale Kontrolle aller Metastasen nicht erreicht werden kann, können insbesondere die lokoregionären Therapieverfahren (transarterielle Chemoembolisation, Radioembolisation) einen Betrag zur Tumorkontrolle und Zytoreduktion leisten. Die Rationale dieser Therapiestrategie basiert auf dem Konzept der „deepness of response“ bzw. Ansprechtiefe. Ein weitestgehendes Zurückdrängen der Tumorerkrankung kann hierdurch potentiell das Gesamtüberleben verlängern, auch wenn darüber hinaus eine unweigerliche Tumorprogression eintritt [18,19].

Die Wachstumskinetik von Tumoren unter einer Chemo- oder Strahlentherapie wird grundlegend durch das Modell des fraktionierten Zelltodes („fractional cell kill“ bzw. „Log cell kill“) beschrieben [20]. Ausgehend von dieser Theorie wurden Hypothesen entwickelt, welche die Tumorkinetik in Zusammenhang mit den verschiedenen Zeitmessungen in der Onkologie wie dem progressionsfreien Überleben (PFS) und Gesamtüberleben (OS) setzen. Grundlage dieser Betrachtungen ist die Annahme, dass eine bestimmte Last an Tumorzellen bzw. die nachfolgende Tumorkachexie für das menschliche Organsystem letal wirkt [21-23]. Entscheidend ist nun gegenüber systemischen Therapien, dass bei einer ausgedehnten Zytoreduktion durch lokale oder lokoregionäre Therapieverfahren zwar kurzfristig ein formaler Progress anhand bildgebender Kriterien eintreten kann (niedriges PFS), die Rückkehr zur initialen, aktiven Tumorlast jedoch überproportional längere Zeiträume erfordert und damit das Gesamtüberleben wie durch eine systemischen Chemotherapie verbessert werden kann (höheres OS) [18].

Durch die zunehmende Verfügbarkeit minimal-invasiver Operationstechniken und lokalablativer Verfahren bekommt dieses Konzept der Ansprechtiefe bzw. „deepness of response“ eine weitere Bedeutung: wenn die Gesamtanzahl an Tumorzellen idealisiert die Prognose des Patienten bestimmt, so könnte eine totale bzw. subtotale Resektion oder Ablation von Metastasen eine ähnliche Effektivität wie mehrere Zyklen einer intensiven Polychemotherapie generieren. Durch die spezifische Dosisdistribution der interstitiellen Brachytherapie ist es insbesondere möglich, selbst große Tumore (> 10cm) bis in den Randbereich zu einem Großteil mit letalen Dosen zu umschließen [24].

Da es sich bei dem Konzept der Ansprechtiefe um eine stark vereinfachte Vorstellung der Tumorbiologie handelt, kann diese idealisierte Annahme nicht

zwingend auf das durchaus große, zytoreduktive Potenzial der interventionellen Verfahren im klinischen Alltag angewendet werden und bedarf weiterer Analysen, um das volle, denkbare Potential zu evaluieren. Für die Ansprechtiefe gibt es erste Publikationen, die einen Überlebensvorteil unter einer systemischen Therapie beschreiben: In einer Studie von Nozawa el a. konnte in einem Kollektiv von 156 Patienten unter Erstlinienchemotherapie beim metastasierten kolorektalen Karzinom bei einem Ansprechen von >45% der Tumormasse ein progressionsfreies Überleben von 16,4 vs. 8,1 Monaten erreicht werden. Das mediane Gesamtüberleben verlängerte sich bei höherer Ansprechtiefe dann überproportional von 30,9 Monaten auf 58,6 Monate, obwohl die folgenden Chemotherapielinien zwischen den Gruppen keine signifikanten Unterschiede aufwiesen [19]. Ähnliche Beobachtungen zur Effektivität eines frühen und tiefen Tumoransprechens konnten bereits auch für das metastasierte Nierenzellkarzinom unter einer Therapie mit Tyrosinkinasehemmern sowie bei der Erstlinienchemotherapie des metastasierten Magenkarzinoms gemacht werden [25,26]. Klinische relevante Beobachtungen bei lokalen Therapien stehen jedoch bisher aus.

2.4 Integration in multidisziplinäre Therapieansätze

Als „vierte Säule“ in der Tumorbehandlung sind mittlerweile fast alle interventionellen Verfahren in den aktuellen Leitlinien zum metastasierten kolorektalen Karzinom (mCRC) als auch zum hepatozellulären Karzinom (HCC) repräsentiert [7].
Der Einsatz einer aggressiven Lokaltherapie wurde bereits im Kapitel 2.2 erwähnt. Die Ergebnisse der CLOCC-Studie beim mCRC zeigen hier deutlich, dass letztlich nicht das alleinige Behandlungspotenzial einer Fachdisziplin entscheidet, sondern die unvoreingenommene Kombination aus Chirurgie und interventioneller Radiologie den entscheidenden Vorteil im Überleben der Patienten erreichen kann, auch wenn die Interpretation der Daten durch das multimodale Konzept erschwert wird [14].
Insbesondere bei der Metastasierung in die Leber haben chirurgische und interventionell-radiologische Therapieverfahren technische Vor- und Nachteile, die sich mitunter günstig ergänzen können:
Tumore mit einer subkapsulären Lokalisation sind chirurgisch gut zugänglich und können parenchymsparend atypisch reseziert werden. Bei einer tieferen Lage im Leberparenchym können unter Umstände technisch aufwändige Resektionen selbst bei kleineren Tumoren nötig werden, während eine bildgeführte Radiofrequenzablation an dieser Stelle lokal begrenzt den Tumor ausschalten kann. Limitierend für die thermischen Ablationsverfahren bleiben jedoch immer der Kühlungseffekt benachbarter Gefäße und die Nähe hitzevulnerabler Strukturen [27-29]. Bei älteren und multimorbiden Patienten kann zudem eine Operabilität der Tumorerkrankung technisch möglich sein, jedoch wäre klinisch mit einer deutlich höheren Morbidität und Mortalität infolge der Operation zu rechnen. Durch den mikroinvasiven Charakter der interventionellen Ablationstechniken kann solchen Patienten noch die Möglichkeit einer nahezu äquivalenten Therapie geboten werden [29-31]. Dies erklärt zugleich die Diskrepanzen in den Ergebnissen zwischen chirurgischer und interventioneller Lokaltherapie, da eine positive Patientenselektion zugunsten der Chirurgie anzunehmen ist [31,32].
Weiterhin verschwindet durch den multimodalen Therapieansatz zunehmend die Grenze zur alleinigen, systemischen Chemotherapie bei nicht vollständig operablen bzw. nicht vollständig abladierbaren Metastasierungskonstellationen. Die Ergebnisse zur ergänzenden Zytoreduktion durch lokalablative (RFA/MWA/iBT) und lokoregionäre Therapien (TACE, Y90-RE) sind jedoch in der Erstlinie gemischt. So konnte im Gegensatz zur CLOCC-Studie eine zusätzliche Y90-Radioembolisation

neben der Erstlinienchemotherapie bei mCRC in den Studien SIRFLOX und FOXFIRE keine Überlebensverlängerung gegenüber Chemotherapie allein erreichen. Lediglich das Tumorfortschreiten in der Leber wurde verzögert [33,34]. Der Einsatz in der Zweitlinientherapie wurde bisher nur in einer Studie von van Hazel et al. in Kombination mit Irinotecan (Progress unter 5-Fluorouracil±Oxaliplatin) untersucht, solide Daten aus großen Patientenkollektiven fehlen jedoch bisher [35,36].
Eine weitere, spezielle Situation im onkologischen Alltag ist die „mixed response“ einer systemischen Tumorerkrankung, bei der ein Teil der Metastasen auf die Systemtherapie anspricht, während ein weiterer Teil eine Progression zeigt [37]. Hintergrund ist die Polyklonalität von Metastasen bzw. die klonale Selektion innerhalb des Zellverbandes durch eine Chemotherapie, die zur Therapieresistenz einiger Metastasen bzw. Zellklone führt [9,38]. Die Häufigkeit dieser Situation auf bildmorphologischer bzw. molekularer Ebene beträgt etwa 25% bzw. 19% [37,38]. Eine Untersuchung nach der adjuvanten Chemotherapie primärer kolorektaler Tumore konnte passend hierzu eine Zunahme an somatischen Genmutationen bei der Intensivierung des Therapieregimes (keine adjuvante Therapie vs. 5-Fluorouracil vs. FOLFOX) nachweisen, die sogar mit einem schlechteren Outcome nach Resektion metachroner Lebermetastasen verbunden war [39]. Aus all diesen Daten zur molekularen Heterogenität von Metastasen lässt sich nun ein bisher nicht tiefgehend untersuchtes Konzept ableiten: Die interventionellen Verfahren bieten in der „mixed response“ die Möglichkeit, mit geringer Belastung des Patienten gezielt progrediente und damit chemoresistente Metastasen auszuschalten. Hierdurch könnte eine sonst nötige Umstellung der Systemtherapie verschoben und das Überleben potentiell verlängert werden.
Im weiteren Krankheitsverlauf muss zudem damit gerechnet werden, dass Patienten bei zunehmender Toxizität der Chemotherapie eine Weiterbehandlung abbrechen oder die verfügbaren Substanzen erschöpft sind [7,40]. Speziell beim kolorektalen Karzinom stellt dann die meist leberdominante Metastasierung die Limitation für das Leben des Patienten dar. In dieser „Salvage“-Situation kann eine interstielle Brachytherapie oder meist die Y90-Radioembolisation zur Zytoreduktion und Überlebensverlängerung eingesetzt werden. Bei leberisolierter oder leberdominanter Metastasierung des kolorektalen Karzinoms konnten so bereits mehrere Studien den Überlebensvorteil durch eine Radioembolisation der Leber zeigen [41,42]. Entscheidend bleibt aber hier die Patientenselektion (siehe **Veröffentlichung 7**).

Eine andere onkologische Situation stellt das hepatozelluläre Karzinom (HCC) dar. Da die Leberzirrhose die weit häufigste Ätiologie für das HCC ausmacht, besteht in den meisten Fällen eine prognostische Konkurrenz zwischen Tumorerkrankung und Lebergrunderkrankung, bei der die Lebererkrankung auch führend sein kann [43-45]. Bei fortgeschrittener Zirrhose mit portaler Hypertension bestehen hohe Risiken für eine chirurgische Therapie, folglich haben frühzeitig lokale Therapien wie die Radiofrequenz-ablation oder Chemoembolisation einen hohen Stellenwert in der Behandlung des HCC erreicht und Einzug in die Leitlinien gefunden [46]. Lediglich die Y90-Radioembolisation ist durch die Heterogenität der fortgeschrittenen Tumorstadien BCLC B und C schwerer einzuordnen [47,48]. Bei weit fortgeschrittener Erkrankung konnte auch aufgrund des teils ungünstigen Studiendesigns (SAHRA und SIRveNIB) bisher kein größerer Überlebensvorteil gegenüber oder mit einer systemischen Therapie verzeichnet werden [49,50]. Für selektierte Subgruppen (z.B. BCLC B2) scheint jedoch ein Überlebensvorteil zu bestehen, der noch in prospektiven Studien bestätigt werden muss [51].
Auch beim cholangiozellulären Karzinom werden im inoperablen Stadium nun multimodale Konzepte untersucht - vornehmlich ist hier die SIRCCA-Studie zu nennen, welche die Y90-Radioembolisation mit der bisherigen Standardchemotherapie (Gemcitabine/Cisplatin) kombiniert (NCT02807181). Das Ende der Rekrutierung und erste Ergebnisse werden im Jahr 2020 erwartet.

3. Technisch-klinische Weiterentwicklungen

3.1 Perkutane Radiofrequenzablation

Die Radiofrequenzablation (RFA) ist ein verbreitetes und etabliertes Verfahren in der Behandlung von lokal begrenzten Tumoren und kann sowohl intraoperativ als auch bildgeführt perkutan angewendet werden. Mit Hilfe von Wechselströmen kann durch die RFA eine thermische Koagulationsnekrose bis zu 5 cm generiert werden [52]. Ähnlich zu den Maßgaben der chirurgischen Resektion soll hierbei ein Sicherheitssaum um den Tumor eingeschlossen werden, der laut Literatur in der Lunge und Leber mindestens 5 mm betragen sollte [53,54]. Sowohl für die Ablation von Lungen- als auch Lebermetastasen sind die besten Langzeitergebnisse daher für Tumordurchmesser bis 3 cm beschrieben, da sich in diesen Fällen der Sicherheitssaum technisch am besten garantieren lässt. Hierdurch werden ein tumorfreies Überleben bei 33,6% der Patienten sowie lokale Tumorkontrollraten von 86,2% nach 5 Jahren erreicht [55,56]. Bei der Beschränkung auf diese Metastasengröße wird in einigen Studien sogar ein Vorteil in der lokalen Kontrolle nach RFA gegenüber der atypischen Resektion (90% vs. 81% Tumorkontrollrate) diskutiert [57]. Das mediane Gesamtüberleben nach intraoperativer oder perkutaner RFA kolorektaler Lebermetastasen wird in verschiedenen Kollektiven mit 24 bis 36 Monaten angegeben (**Veröffentlichung 2**).

In einer eigenen Subgruppe von 60 Patienten mit kolorektalen Leber- und Lungenmetastasen konnte in Abhängigkeit des Alters und der Komorbidität ein Gesamtüberleben von 24,0 bis 26,7 Monaten aufgezeigt werden (**Veröffentlichung 11**) und ist mit den publizierten Ergebnissen vergleichbar. Anzumerken ist hierbei der Anteil von 33,5% alter Patienten > 70 Jahre sowie 16,2% schwer komorbider Patienten am Gesamtkollektiv, welche eine positive Patientenselektion eher ausschließt und Werte am unteren Rand des genannten Bereichs erklären kann. Nach Radiofrequenzablation von Lungentumoren verschiedener Entitäten im Universitätsklinikum Magdeburg wurde ein medianes Gesamtüberleben von 27 Monaten bei einer lokalen Tumorkontrolle von 85,3% beobachtet (**Veröffentlichung 9**). Als wesentlicher Einflussfaktor auf den Therapieerfolg zeigte sich hier abermals der Tumordurchmesser, während Abstände zu Pleura, Bronchialsystem und Gefäßen keinen Einfluss hatten. Bei Metastasen bis 1 cm ließ sich sogar eine lokale Tumorkontrollrate von 92,7% verzeichnen. Die Komplikationshäufigkeit war mit 3

Majorkomplikationen (drainagepflichtiger Pleuraerguss n=2; Hautverbrennung n=1) zur Literatur vergleichbar (**Veröffentlichung 2, 9**).
Beim Nierenzellkarzinom wird häufig eine Größe von 4 cm als technische Grenze für eine RFA verwendet, da diese dem Tumorstadium T1a entspricht. Trotzdem zeigen sich auch hier eine Größe bis 3 cm und ein Sicherheitssaum von 5 bis 10 mm als wesentliche Erfolgsfaktoren (**Veröffentlichung 17**), die somit übergreifend für die Radiofrequenzablation in Lunge, Leber und Nieren gelten dürfen. Während sich die Tumorgröße von 3 bis 4 cm durch die technischen Limitationen der Radiofrequenzablation begründen lässt, stellen die beste Erklärung für den Sicherheitsabstand mikroskopische Tumorzellansammlungen (Mikrometastasen) in der Umgebung des primären Tumors bzw. der Metastase dar.
Diese lassen sich exemplarisch bei mehr als der Hälfte der Lebermetastasen kolorektaler Karzinome identifizieren und treten zu 95% innerhalb von 10 mm um den makroskopischen Tumorrand auf [58,59].

3.2 Interstitielle Brachytherapie

Die interstitielle Brachytherapie (iBT) ist ein katheterbasiertes Bestrahlungsverfahren zur Ablation von Tumoren und erfolgt in parenchymatösen Organen wie der Leber in zwei wesentlichen Schritten: Zuerst ist eine Implantation der Bestrahlungskatheter im Zielorgan erforderlich, die meist durch einen interventionell tätigen Radiologen unter Bildführung durch CT oder MRT vorgenommen wird. Anschließend erfolgt im Anschluss die eigentliche Strahlenbehandlung im Afterloading-Verfahren durch den Strahlentherapeuten mit einer Iridium-192-Quelle nach vorangegangener dreidimensionaler Bestrahlungsplanung [60].

Aufgrund der hohen Dosisleistung der Quelle (High-dose-rate Brachytherapie, >12Gy/h) können in kurzer Zeit Bestrahlungsdosen im Zielvolumen erreicht werden, die den Anspruch an eine vollständige Ausschaltung aller Tumorzellen erheben („Radioablation“)[61]. Das häufigste Anwendungsgebiet in der eigenen Klinik sind Lebermetastasen kolorektaler Karzinome (**Veröffentlichung 2**).

3.2.1 Therapeutische Anwendung

Einen wesentlichen Vorteil der interstitiellen Brachytherapie gegenüber thermischen Ablationsverfahren wie der Radiofrequenzablation stellt die Unabhängigkeit von Kühlungseffekten benachbarter Gefäße dar (Heat-sink-Effekt) [27], ebenso ist die Nähe zu hitzevulnerablen Strukturen wie Gallengängen im Hilusbereich der Leber in den meisten Fällen nicht relevant [62]. Weiterhin gibt es keine technische Größenlimitation des zu bestrahlenden Tumors und gegenüber der stereotaktischen Bestrahlung besteht durch die feste Platzierung der Katheter in der Zielläsion kein Einfluss durch die Atemexkursion [24,63].

Für eine möglichst effektive Tumorablation ist die Lage der implantierten Katheter von höchster Wichtigkeit. Üblicherweise wird zur Punktion und folgenden Einbringung der Brachytherapiekatheter als Bildführungsmodalität die Computertomographie verwendet, die besonders im Fall von kleinen Zielläsionen visuellen Einschränkungen unterliegt [64]. Bei komplexen Eingriffen steigt hierdurch auch die Strahlenexposition des durchführenden Radiologen in Abhängigkeit von dessen Erfahrungsgrad [65,66]. Aus diesen Gründen wurde in einer Pilotstudie die Möglichkeit untersucht, die Punktion und Katheteranlage in der CT-Fluoroskopie durch den Ultraschall zu ergänzen oder zu ersetzen (**Veröffentlichung 12**). Bei 12 Patienten mit 16 Tumoren der Leber oder Nieren konnte in 12 Läsionen die Katheterimplantation erfolgreich

unter sonographischer Führung erfolgen, konkret betraf dies 23 von 28 Bestrahlungskathetern. Nachgewiesen werden konnte bereits an diesem kleinen Kollektiv die Reduktion der Fluoroskopiezeit im CT (14,5s vs. 105,5s pro Eingriff bei Hinzunahme der Sonographie, $p<0,006$). Hinweise gab es für die bessere Sichtbarkeit der Leber- und Nierentumore im Ultraschall gegenüber der CT, obgleich diese nicht statistisch signifikant waren und sich mit Erfahrungen bei der Radiofrequenzablation von Lebertumoren decken [67]. Darüber hinaus besteht technisch auch die Möglichkeit, die Punktion und Katheterimplantation im offenen MRT durchzuführen, wobei diese Geräteausstattung nur in wenigen Institutionen zur Verführung steht und spezifische Kathetermaterialien zur Anwendung kommen müssen [68,69].

Aus strahlentherapeutischer Sicht kann die interstitielle Brachytherapie an verschiedene Tumorentitäten und Organsysteme adaptiert werden, da über das linearquadratische Modell die Dosimetrie der externen Strahlentherapie zur hypofraktionierten Brachytherapie umgerechnet werden kann [70,71]. Hierdurch ist es möglich, strahlenbiologische Dosisverschreibungen von der perkutanen Strahlentehrapie bei Plattenepithelkarzinomen auf die interstitielle Brachytherapie zu übertragen und in eine erfolgreiche, klinische Anwendung bei Metastasen des Ösophagus- sowie Analkarzinoms umzusetzen (**Veröffentlichung 10, Veröffentlichung 14**). In den beiden Studien wurden lokale Tumorkontrollraten von 85,7% bzw. 97,4% als technisches Erfolgskriterium erreicht. Die klinischen Implikationen der Studien werden im Kapitel 4.4 und 4.5 ausführlicher behandelt.

Im Falle des inoperablen, hepatozellulären Karzinoms (HCC) kommt der interstitiellen Brachytherapie eine Bedeutung bei der Behandlung großer solitärer sowie multifokaler Knoten zu [72,73]. Durch die Größenlimitation der thermischen Ablationsverfahren stehen für das HCC im Stadium BCLC B sonst nur die transarteriellen Embolisationsverfahren wie die Chemoembolisation (TACE) zur Verfügung [74]. Diese weisen jedoch eigene Einschränkungen im notwendigen Gefäßzugang durch anatomische Normvarianten und extrahepatische Tumorversorgung auf und zeigen eine limitierte Wirksamkeit bei großen und zahlreichen HCC-Knoten [75-77]. Zum Vergleich des Stellenwertes der interstitiellen Brachytherapie gegenüber der TACE wurde daher eine randomisierte Phase-2-Studie durchgeführt (**Veröffentlichung 15**): Bei 37 Patienten erfolgte die Behandlung von 1 bis 3 Tumoren mit einer Größe von 2,1 bis 6,6 cm primär mittels

Brachytherapie, zur Radioablation wurde für das CTV (Clinical target volume) aufgrund der genannten Vorstudien eine Dosis von 15Gy gewählt. Zum Erreichen der Tumorkontrolle waren im Mittel 2,5 ± 1,6 Behandlungen mittels Brachytherapie (n=37) notwendig, bei der Kohorte mit TACE (n=40) waren mit 4,0 ± 3,2 signifikant mehr Sitzungen erforderlich. Durch technische Limitationen der TACE erfolgte bei mehr als einem Drittel der Patienten im TACE-Arm (14/40; 35%) ein Cross-over zur Brachytherapie, um eine lokale Tumorkontrolle zu erlangen. Es lässt sich somit folgern, dass die interstitielle Brachytherapie technisch robuster in der Anwendung beim HCC im Vergleich zur TACE ist.

Neben der Sicherheitsanalyse in einer Phase-1-Studie konnte bei der ersten, ausführlichen Anwendungsbeschreibung der Brachytherapie bei Nierentumoren ebenfalls die lokale Tumorkontrollerate bestimmt werden (**Veröffentlichung 20**): für eine Kohorte von 20 Tumoren (Nierenzellkarzinome n=18, Nierenmetastasen n=2) betrug die lokale Kontrollrate bei einer Ablationsdosis von 15Gy für das CTV primär 85%. Durch die erneute Behandlung von zwei Rezidiven mit einer Dosiseskalation auf 20Gy konnte eine sekundäre Kontrolle bei 95% der Nierentumore erreicht werden. Hierbei waren sechs Tumore (30%) aufgrund ihrer Nähe zu zentralen Hilusstrukturen und fünf Tumore (25%) durch ihre Größe (>4cm, Stadium T1b) nicht einer effektiven, thermischen Ablation zugänglich [78]. In weiteren Untersuchungen muss folglich geklärt werden, welche technischen Limitationen für die Brachytherapie der Niere gelten müssen und welche Ablationsdosis eine günstige Tumorkontrolle bei Erhalt der Nierenfunktion sicherstellt. Die Sicherheitsanalyse dieser Studie wird unter anderem im folgenden Kapitel diskutiert. Auch für Lebermetastasen des Nierenzellkarzinoms wurde die interstitielle Brachytherapie als Ablationsverfahren untersucht (**Veröffentlichung 18**) und konnte mit 92,6% eine ähnliche lokale Kontrollrate wie bei den Primärtumoren der Niere aufzeigen (14 Patienten mit 54 Metastasen). Als Zieldosis für das CTV wurde analog 15Gy gewählt. Die mittlere Metastasengröße betrug 2,9 cm, wobei einzelne Metastasen bis zu 13,9 cm Größe behandelt wurden und damit für einen Teil der Patienten ein thermisches Ablationsverfahren als Alternative nicht in Frage gekommen wäre.

Einen Überblick über die erwähnten Veröffentlichungen gibt **Anhang** Tabelle 2.

3.2.2 Strahlenassoziierte Nebenwirkungen

Da die interstitielle Brachytherapie typischerweise in einer einzigen Fraktion angewendet wird, können hohe Punktdosen an Nachbarorganen zu strahlenbiologischen Restriktionen oder Komplikationen führen. Gerade bei subkapsulär lokalisierten Lebertumoren besteht oft ein direkter Kontakt zum benachbarten Magen und Duodenum sowie Dünn- oder Dickdarm.

In einer Kohorte von 192 Patienten mit primären und sekundären Lebermalignomen erfolgten 343 Tumorbehandlungen mittels Brachytherapie, hiervon waren bei 57 Patienten (29,7%) bzw. 72 Interventionen (21,0%) gastrointestinale Nachbarorgane mit mindestens 1 Gy / cm^3 belastet. Bei 3 Patienten (4,2%) führte dies zu einem Ulkusleiden (**Veröffentlichung 6**). Es wurde nachfolgend ein Schwellwert für die Punktdosis von 14 Gy ermittelt, der bei Überschreitung signifikant das Auftreten eines gastrointestinalen Ulkus vorhersagen konnte. Ein vergleichbarer Grenzwert von 15.5 Gy wurde von Streitparth et al. ermittelt, womit in der klinischen Anwendung 15 Gy als maximale Punktdosis am Gastrointestinaltrakt betrachtet werden können [79].

Da die Nähe zu radiosensitiven Darmstrukturen eine häufige Limitation für das Erreichen einer ablativen Zieldosis bei der interstitiellen Brachytherapie darstellt, wurde eine interventionelle Technik zur Distanzierung der Risikostrukturen entwickelt. Techniken aus dem Gebiet der thermischen Ablationsverfahren wie die Hydrodissektion und Gasinsufflation unterliegen dynamischen Verteilungsprozessen im Abdominalraum, wodurch im Zeitintervall von der Katheterimplantation bis zur Brachytherapie die Verlässlichkeit der Bestrahlungsplanung nicht sichergestellt werden kann [80]. Durch das interventionelle Einbringen von angiographischen Ballonkathetern (20 mm bzw. 27 mm Durchmesser) kann eine zeitlich stabile Distanzierung von Darmstrukturen in der Nähe der Ablationszone (typischerweise an der Leberkapsel) erreicht werden (**Veröffentlichung 19**). In dieser Fallserie mit 31 Patienten wurde mindestens ein Ballonkatheter zwischen Zielstruktur und Risikoorgan implantiert und neben der eigentlichen Bestrahlungsplanung eine simulierte Dosimetrie ohne Distanzierung erstellt. Die mittlere Punktdosis am Risikoorgan konnte durch diese neue Technik von 16 Gy auf 12,6 Gy gesenkt und somit die zuvor genannten Dosisgrenzwerte für den Gastrointestinaltrakt (Punktdosis maximal 15 Gy) eingehalten werden.

Ein weiteres Problem hoher Punktdosen an benachbarten Strukturen stellt die Brachytherapie zentraler Lebertumore mit Exposition der großen Gallenwege dar.

Bei 102 Patienten mit einer Exposition der zentralen Gallenwege durch eine Punktdosis ≥1Gy wurde das Auftreten einer Cholestase retrospektiv analysiert (**Veröffentlichung 13**). Bei 22 Patienten (22%) kam es in einem medianen Zeitraum von 17 Monaten zu einer morphologisch sichtbaren Cholestase. In deren Folge musste bei 18 Patienten eine perkutan-transhepatische Cholangiodrainage (PTCD) oder eine endoskopisch-retrograde Cholangiographie (ERC) mit interner Ableitung erfolgen. In dieser Patientengruppe traten im Verlauf auch signifikant häufiger Cholangitiden und biliäre Abszedierungen auf (18% vs. 2,5%; p=0,029). In einer ROC-Analyse ließ sich ein optimaler Grenzwert für die Punktdosis an den zentralen Gallenwegen von 20,8 Gy ermitteln (Sensitivität 59%; Spezifität 41%; p=0,028), der signifikant die Entwicklung einer Cholestase vorhersagen kann. Vergleicht man die korrespondierende biologische Äquivalenzdosis (BED_3: 165 Gy) mit ähnlichen Verfahren wie der Stereotaxie (SBRT), so werden hier Äquivalenzdosen an den zentralen Gallenwegen unterhalb der ermittelten Grenzdosis berichtet (exemplarisch BED_3: 147 Gy) [81,82]. In diesen Patientenkollektiven traten entsprechend auch keine biliären Komplikationen auf. Somit scheint der ermittelte Grenzwert von 20,8 Gy unter Beachtung der statistischen Signifikanz und trotz der eher geringen Sensitivität und Spezifität plausibel.

Neben der Dosisexposition von benachbarten Organen und Strukturen kommt auch den radiogenen Effekten auf das gesunde Parenchym der eigentlichen Zielorgane eine Bedeutung zu. Dies betrifft in den meisten Fällen die Leber oder die Nieren, die durch die interstitielle Brachytherapie von hepatischen bzw. renalen Tumoren zumindest in der direkten Umgebung signifikanten Strahlendosen ausgesetzt sind. Hierbei ist zu beachten, dass die Effekte auf das gesunde Organparenchym neben dem Tumor zwar durch das linearquadratische Modell abgeschätzt werden können, sich jedoch durch die Spezifika der HDR-Brachytherapie (Einzelfraktion mit einem steilen Dosisgradienten) nicht exakt vorhersagen lassen [70,71]. Weil die CT-gestützte Brachytherapie bisher zum Großteil in der Leber angewendet wird, liegen hier die meisten Erfahrungen vor [61]. Insbesondere die radiogene Leberfunktionseinschränkung (radiation-induced liver disease, RILD) nach Brachytherapie ist hinsichtlich der Dosisbeziehung gut untersucht und kann durch die MRT mit dem hepatozytenspezifischem Kontrastmittel Gd-EOB-DTPA visualisiert werden [83,84]. Ähnliche Zusammenhänge bestehen bei der stereotaktischen Radiotherapien [85].

In der Arbeit zu Komplikationen der Brachytherapie in der Leber (**Veröffentlichung 6**) zeigten sich zunächst häufig Leberenzymwerterhöhungen. Bei nur einem Fall von 192 Patienten (0,5%) kam es durch wiederholte Brachytherapien von HCC-Manifestationen in einer voroperierten Leber mit Steatohepatitis zu einer hepatischen Dekompensation, die sich innerhalb von 7 Monaten rekompensieren ließ. Eine klinisch signifikante Leberfunktionseinschränkung ist somit nach Brachytherapie offensichtlich selten. Für Patienten mit einem erhöhten Risiko (z.B. geringes Lebervolumen, Leberzirrhose, hepatotoxische Chemotherapie) steht zudem eine medikamentöse Prophylaxe der RILD zur Verfügung. In einer prospektiv-randomisierten Studie (**Veröffentlichung 5**) wurde durch die Bildfusion aus Bestrahlungsplanungs-CT und Nachsorge-MRT die exakte Grenzdosis des Leberparenchymschadens nach interstitieller Brachytherapie von kolorektalen Lebermetastasen determiniert und in Beziehung zu einer über 8 Wochen applizierten Medikation mit Ursodeoxycholsäure, Enoxaparin und Pentoxifyllin untersucht. Durch die Medikamentengabe liest sich die im posttherapeutischen MRT sichtbare Leberfunktionsschädigung in der Umgebung der behandelten Lebermetastasen sowohl in der Ausprägung als auch generellen Inzidenz signifikant reduzieren. Die Grenzdosis des Leberparenchymschadens und somit auch die Strahlentoleranz des gesunden Lebergewebes wurden folglich medikamentös von 14,64 Gy auf 19,06 Gy erhöht. Somit steht mit diesen Phase-II-Daten eine pharmakologische Prophylaxe zur Verfügung, die zumindest im Fall von klinisch evidenter oder drohender RILD eingesetzt werden kann. Ausführlich wird das Thema noch im **Kapitel 3**, Abschnitt 3.3.3 behandelt.

Für die interstitielle Brachytherapie von Nierentumoren lagen bisher keine ausführlichen Daten zur Nierenfunktion vor. In einer prospektiven Phase-1-Studie wurde daher die Sicherheit der Brachytherapie in der Niere evaluiert (**Veröffentlichung 20**). Von 16 untersuchten Patienten hatten bereits jeweils zwei Patienten eine kontralaterale Nephrektomie und ipsilaterale partielle Nephrektomie. Als Vorerkrankungen bestanden polyzystische Nieren und Hufeisennieren bei jeweils einem Patienten. In dieser Kohorte mit negativ prädisponierenden Faktoren trat in einem medianen Nachsorgezeitraum von 22,5 Monaten bei nur einem Patienten eine Dialysepflicht ein, wobei dieser bereits individuell mit einer Radiofrequenzablation der kontralateral Nieren und einer prätherapeutischen Niereninsuffizienz °IV vorbelastet war. Beobachtet wurde weder eine signifikante Verschlechterung der glomerulären

Filtrationsrate (nach CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration) noch eine Verschlechterung des Niereninsuffizienzstadiums (nach KDOQI, Kidney Disease Outcomes Quality Initiative) im Median des Patientenkollektivs. In der szintigraphischen Messung der tubulären Extraktionsrate (TER) wurde ein Funktionsrückgang der durch die Brachytherapie exponierten Niere dokumentiert, während die kontralaterale einen kompensatorischen Funktionszuwachs verzeichnete. Auch wenn die exakte Wirkung der Strahlenexposition der Niere bislang wenig untersucht ist, so scheint die Schädigung des gesunden Nierenparenchyms bei der interstitiellen Brachytherapie ähnliche Hypertrophieeffekte wie bei Nephrektomie auszulösen und könnte auf eine Reduktion der funktionell verfügbaren Nephrone basieren [86,87]. Eine Zusammenfassung der radiogenen Nebenwirkungen der Brachytherapie gibt der **Anhang** in Tabelle 3.

3.2.3 Interventionelle Komplikationen

Zusätzlich zu den Nebenwirkungen der hochdosierten Bestrahlung besteht bei der interstitiellen Brachytherapie das Komplikationsrisiko durch die interventionelle Katheteranlage. Hierbei bestehen die typischen Risiken der bildgeführten Punktion und Ablation (z.B. Blutung, Infektion, Pneumothorax) [88]. Bei der Analyse von 192 Patienten mit 343 interstitiellen Brachytherapien der Leber (**Veröffentlichung 6**) wurden 10 schwere punktionsbedingte Komplikationen (2,9%) Grad 3/4 anhand der CTCAE-Klassifikation (Common Terminology Criteria for Adverse Events) beobachtet. Hierbei handelte es sich um fünf Blutungskomplikationen, vier Leberabszesse und eine akute Gallenwegsobstruktion. Eine signifikante Häufung an Blutungen betraf Patienten mit einem hepatozellulären Karzinom bzw. einer Leberzirrhose. Bei der Sicherheitsanalyse zur Brachytherapie der Niere (**Veröffentlichung 20**) wurde als interventionelle Komplikation eine Interkostalarterienblutung entsprechend eines punktionsbasierten Risikos von 2,3% beobachtet, welches sich mit den oben genannten Daten deckt.
Eine späte Komplikation der interstitiellen Brachytherapie ist die Dislokation von Tumorzellen entlang des Katheters, welche zu einer Metastasenentstehung im Stichkanal führen kann. Exemplarisch wurde dies anhand des hepatozellulären Karzinoms (HCC) untersucht (**Veröffentlichung 16**). Für andere, bildgeführte Eingriffe wie die Leberbiopsie und Radiofrequenzablation wurde bereits das Risiko einer Stichkanalmetastasierung beschrieben. In einer Metanalyse von Stigliano et al.

2007 konnte bei der Auswertung von 41 wissenschaftlichen Arbeiten über die perkutane Punktionen und Ablation des HCC eine Gesamthäufigkeit von 1,27% bestimmt werden, wobei je nach Interventionsverfahren eine Häufigkeit zwischen 0,61% bis 2,29% beschrieben wurde [89]. Da beim hepatozellulären Karzinom im frühen Stadium (BCLC 0/A) eine Indikation für die Lebertransplantation besteht und die Radiofrequenzablation zur Überbrückungstherapie („Bridging“) angewendet wird, kommt der Stichkanalmetastasierung hier eine besondere Bedeutung zu [74,90]. Weiterhin kann nicht in allen Fällen die Diagnose eines HCC (z.B. außerhalb der Leberzirrhose) nicht-invasiv über die Bildgebung gestellt werden und somit besteht bereits bei der Biopsie das Risiko einer Zellverschleppung vor der Indikationsstellung zur Resektion oder Lebertransplantation [91,92]. Bei der Brachytherapie des HCC konnte retrospektiv eine Stichkanalmetastasierung von 1,5% pro Katheter und 3,9% pro HCC bei einer Läsionsgröße von 1,0 bis 16,6 cm beobachtet werden. Aufgrund einer aufwendigen Bildfusion bei der Datenerhebung konnten in dieser Arbeit (**Veröffentlichung 16**) auch intrahepatische Stichkanalmetastasen identifiziert werden, die sonst in der Literatur kaum Beachtung finden [93]. Acht von neun intrahepatischen Metastasen konnten erfolgreich erneut mittels interstitieller Brachytherapie behandelt werden. Bezogen auf extrahepatische Stichkanalmetastasen lag die Häufigkeit bei 0,3% je Katheter und kann somit als vergleichbar mit den Daten der RFA gelten [94]. Folglich kann die Brachytherapie auch in Ergänzung zur RFA oder Chemoembolisation als Überbrückungsverfahren zur Lebertransplantation angewendet werden [95]. Als Resultat dieser Arbeit erfolgt nun analog zur thermischen Ablation des Zugangswegs bei RFA auch bei der Brachytherapie einer Radioablation des Katheterverlaufs mit einer Dosis von 15 Gy als neuer Klinikstandard.
Die interventionellen Komplikationen bei der interstitiellen Brachytherapie sind im **Anhang** in Tabelle 4 zusammengefasst.

3.3 Transarterielle Radioembolisation

Bei der Radioembolisation bzw. selektiven internen Radiotherapie (SIRT) handelt es sich um ein bisher auf die Leber beschränktes Therapieverfahren für die Behandlung nicht resektabler Malignome. Dabei wird über einen angiographischen Katheter an Glas- oder Kunstharzmikrosphären gebundenes Yttrium-90 (Y90) als therapeutisch wirksamer Betastrahler in die Leberarterien eingebracht. Ausgenutzt wird die vorzugsweise arterielle Versorgung von Lebertumoren, wohingegen das gesunde Leberparenchym hauptsächlich über die Pfortader versorgt wird und somit eine günstige Nukliddistribution in der Leber erreicht werden kann [96,97]. Durch den synergistischen Effekt aus Embolisation und Bestrahlung wird eine loko-regionäre Tumorkontrolle in der Leber angestrebt, die jedoch in den allermeisten Fällen nicht einer Ablation wie bei der Radiofrequenzablation oder interstitiellen Brachytherapie gleichkommt. Entsprechend qualifizieren sich hierfür Patienten, die aufgrund der hepatischen Tumorverteilung technisch nicht für ein ablatives Therapieverfahren zugänglich sind (**Veröffentlichung 2**).

Im Nachfolgenden wird insbesondere auch über die Interaktion der Y90-Radioembolisation mit dem gesunden Leberparenchym referiert. Eine Zusammenfassung der wichtigsten Ergebnisse der folgenden drei Unterkapitel gibt der **Anhang**, Tabelle 5.

3.3.1 Radioembolisation und Leberfunktion

Trotz der dualen Blutversorgung der Leber kann eine Y90-Radioembolisation zu einer signifikanten Einschränkung der Leberfunktion führen. Die Strahlenwirkung im gesunden Leberparenchym wird allgemein als Strahlenhepatitis bzw. „radiation induced liver disease“ (RILD) bezeichnet und ist klinisch vorangig durch einen Aszites ohne Ikterus charakterisiert, welcher etwa zwei Wochen bis vier Monate nach Strahlenexposition auftritt [83]. Histopathologisch imponiert die Erkrankung durch einen Verschluss der kleinen Lebervenen und Sinusoide, wodurch sich in frühen Untersuchungen der Begriff „veno-occlusive disease“ (VOD) geprägt hat [98,99]. Eine ähnliche Pathogenese läuft auch bei der Leberfunktionsschädigung durch zytotoxische Chemotherapie bzw. durch kombinierte Chemo- und Radiotherapie ab, wie sie bei myeloablativen Konzepten im Rahmen einer Stammzelltransplantation zu finden ist und dort als „combined modality induced liver disease“ (CMILD) bezeichnet wird [83,100,101].

Die offensichtlich gemeinsame Endstrecke dieser sinusoidalen Obstruktion wird in der jüngeren Literatur auch mit dem Begriff „sinusoidales Obstruktionssyndrom“ beschrieben (sinusoidal obstruction syndrom, SOS) [102]. Trotzdem treten feine Unterschiede in der klinischen Präsentation zwischen den verschiedenen Ätiologien der Leberfunktionsschädigung auf. Bei der Y90-Radioembolisation besteht mit Ikterus und Aszites, einer Erhöhung des Serumbilirubins sowie fast keine laborchemischen Änderung der Transaminasen ein Symptomkomplex, der deutlich größere Gemeinsamkeiten mit der CMILD als mit der eigentlich anzunehmenden RILD aufweist. Dementsprechend wurde speziell der Begriff „radioembolization induced liver disease“ (REILD) geprägt [103]. Als Risikokollektiv für eine REILD konnten bei dieser Arbeit von Sangro et al. Patienten mit geringerem Alter, geringerem Body-Mass-Index, höherer Vorbelastung mit zytotoxischer Chemotherapie und geringerer Tumorlast in der Leber identifiziert werden. Insgesamt traten die typischen Zeichen der REILD bei etwa 20% der Patienten auf, die wie zum Zeitpunkt der Arbeit (2008) üblich in einer Sitzung eine Behandlung der gesamten Leber erhielten. Allen Fällen war gemeinsam, dass entweder eine Leberzirrhose oder eine ausgedehnte Vorbehandlung mit zytotoxischer Chemotherapie vorlag. In einer eigenen Arbeit bestätigte sich die vorbeschriebene Häufigkeit in 3 von 17 Patienten (17,6%), die eine manifeste REILD nach bilobärer Radioembolisation entwickelten (**Veröffentlichung 1**). In Folge dieser Beobachtung wurde ein alternatives Vorgehen etabliert: unter Ausnutzung der Leberarterienanatomie wurden die Y90-Radioembolisation auf den rechten und linken Leberlappen aufgeteilt und in einem zeitlichen Abstand von 4 bis 6 Wochen behandelt [104,105]. Nach dieser sequenziellen Radioembolisation trat kein Fall einer klinisch manifesten REILD auf. Ebenso konnte das Auftreten schwerer Nebenwirkungen (CTCAE °III/°IV) mit 14 Ereignissen bei 17 Patienten nach bilobärer Radioembolisation deutlich reduziert werden. Nach sequenzieller Radioembolisation waren lediglich 2 Ereignisse bei ebenfalls 17 Patienten zu verzeichnen ($p<0.05$). Weiterhin konnte der für die REILD typische Anstieg des Serumbilirubins nur bei der Gruppe der bilobären Radioembolisation beobachtet werden (52,3 vs. 18,7 µmol/l; $p=0.012$). Da im zeitlich versetzt behandelten Leberlappen auch kein signifikanter Tumorzuwachs innerhalb von 4 bis 6 Wochen auftrat, wurde als Resultat dieser Daten die sequenzielle Radioembolisation als klinischer Standard bei chemotherapeutisch vorbehandelten

Patienten in der Klinik für Radiologie und Nuklearmedizin in Magdeburg etabliert und in fast allen Behandlungszentren in der europäischen Union übernommen.
Bei den häufigsten primären und sekundären Lebertumoren wird die Y90-Radioembolisation im weit fortgeschrittenen Stadium eingesetzt und kann eine zeitlich befristete Tumorstabilisierung in einem Bereich von 3 bis 9 Monaten erreichen [106-108]. Aufgrund dieser Positionierung als Salvage-Therapie nach Erschöpfung aller konventionellen Therapieoptionen wird die Y90-Radioembolisation üblicherweise nur einmalig pro Patient eingesetzt. In seltenen Fällen mit einer sehr günstigen Tumorbiologie bzw. sehr gutem, initialen Therapieansprechen stellt sich jedoch Frage, ob eine Wiederholung der Radioembolisation möglich und sicher ist (**Veröffentlichung 4**). In einem Untersuchungszeitraum von vier Jahren traf diese Situation auf 21 Patienten zu, die mindestens drei lobäre Eingriffe erhielten bzw. in mindestens einem Leberlappen mehrfach radioembolisiert worden nachdem die erste Therapie ein Ansprechen zeigte. Es wurden bis zu fünf Y90-Radioembolisationen mit einer Gesamtaktivität aller Interventionen von 1,55 bis 4,15 GBq durchführt. Eine klinisch ersichtliche REILD trat bei keinem dieser Patienten auf, schwere Nebenwirkungen (CTCAE °III/°IV) traten bei 13% der Patienten auf. Im gesamten Beobachtungszeitraum konnte innerhalb des 95%-Konfidenzintervalls keine Bilirubinerhöhung über den Normwert festgestellt werden. Folglich stellt die Y90-Radioembolisaton bei sequenzieller Durchführung und unter Beachtung bekannter Risikofaktoren für eine REILD eine sichere Therapieoption bei fortgeschrittenen Lebertumoren dar [103,109].
Eine zusätzliche Risikostratifizierung ist über die Bestimmung der Tumoraktivität anhand der systemischen Inflammation denkbar [110,111]. Die Messung von Zytokinen kann jedoch nicht nur eine prätherapeutische Situation beschreiben, sondern auch ein Messinstrument für die systemischen Wirkungen der Y90-Radioembolisation darstellen [112]. Bei 34 konsekutiven Patienten wurden daher die Interleukine (IL) 1,2,4,6 und 8 sowie das C-reaktive Protein (CRP), der Tumornekrosefaktor alpha (TNFα) sowie das Interferon gamma (IFγ) bestimmt (**Veröffentlichung 8**). Zunächst ließ sich ein hyperakuter Anstieg des IL-6 drei Tage nach Y90-Radioembolisation verzeichnen (16,8 zu 54,6 pg/ml; p=0,003). Längerfristige Veränderungen standen jedoch in keinem Zusammenhang zu einem klinischen Endpunkt wie dem Therapieansprechen oder Überleben. In einer ROC-Analyse konnten letztlich die prätherapeutischen Werte für IL-6 und IL-8 für ein

Vorhersagemodell für Leberfunktion und Überleben genutzt werden. Ein Grenzwert von 6,53 pg/ml für das IL-6 konnte mit einer Sensitivität von 83,3% sowie einer Spezifität von 86,7% eine Leberfunktionsstörung nach Y90-Radioembolisation vorhersagen. Weiterhin konnten sowohl dieser Grenzwert als auch das IL-8 mit einer Grenze von 60,8 pg/ml signifikant das Überleben schätzen. Das Überschreiten beider Grenzwerte war in einer Cox-Regression signifikant mit einem schlechteren Gesamtüberleben assoziiert. Somit kann die vorbestehende, systemische Inflammation (mit den Surrogatparametern IL6 und IL-8) aufgrund der Tumorerkrankung zur individuellen Indikationsstellung bei der Y90-Radioembolisation genutzt werden. Gleichartige Beobachtungen – insbesondere mit ähnlichen Grenzwerten für das IL-6 von 5 und 6,77 pg/ml – konnten auch für andere Tumorlokalisationen und onkologische Therapien gemacht werden und bestätigen das Potential weiterer Analysen auf diesem Gebiet [113,114].

3.3.2 Hypertrophieinduktion durch radiogene Leberfunktionseinschränkung

Im Jahr 2008 berichteten Jakobs et al. über die Änderung der Lebervolumina infolge einer sequenziellen Y90-Radioembolisation [115]: Der erstbehandelte Leberlappen zeigt eine Volumenreduktion um 8,9%, während der zeitlich versetzt behandelte Leberlappen eine Volumenzunahme um 21,2% aufwies. Das Gesamtlebervolumen wurde durch die Y90-RE ebenfalls reduziert, weiterhin konnte eine Zunahme des Milzvolumens sowie des Pfortaderdurchmessers beobachtet werden. Interpretiert wurde dies als Ausdruck eines steigenden Pfortaderdrucks durch eine radiogen induzierte Fibrose. Diese Auffälligkeiten konnten in einer eigenen Arbeit bestätigt werden (**Veröffentlichung 1**): nach sequenzieller Y90-Radioembolisation zeigte sich eine signifikante Volumenreduktion des erstbehandelten Leberlappens (maximal -18%), während der zweitbehandelte Leberlappen signifikant im Volumen zunahm (maximal +25%). Korrespondierend viel ein Anstieg des Milzvolumens auf (maximal +64%), während die Zunahme des Pfortaderdiameters (maximal +17%) nur nach einer Ganzleberbehandlung zu beobachten war. In einer Arbeit von Paprottka et al. konnten diese volumetrischen Auffälligkeiten bestätigt werden, da gleichsam eine generelle Abnahme des Lebervolumens sowie eine Zunahme von Milzvolumen und Pfortaderdurchmesser gesehen wurde [116]. Eine Ursache dieser Veränderungen scheint das bereits im vorangegangenen Kapitel angesprochene, sinusoidale

Obstruktionssyndrom (SOS) bzw. die venookklusive Erkrankung (VOD) zu sein, die letztlich immer in einer auch geringeren Form abzulaufen scheint, dabei aber nicht als REILD klinisch manifest wird [103,117]. Die radiogen induzierte Kongestion und Fibrose der Sinusoide und kleinen Zentralvenen führt rheologisch zu einer Druckerhöhung im Pfortadersystem, die offensichtlich eine Erweiterung des zentralen Pfortaderdurchmessers sowie ein stauungsbedingtes Anschwellen der Milz hervorrufen kann. Für diese Theorie spricht insbesondere, dass der Effekt bei Y90-Radioembolisation der gesamten Leber in einer Sitzung am deutlichsten erscheint, da keine Kompensation durch einen zeitversetzt behandelten Leberlappens erfolgen kann. Der Volumeneffekt in der Leber selbst ist ebenfalls über die Endstrecke der venookklusiven Erkrankung zu erklären, die letztlich zu einer irreversiblen Fibrose führt [83,98]. Der isoliert beobachtete Volumenzuwachs des linken Leberlappens nach Y90-Radioembolistion des rechten Leberlappens gab den Anstoß, weitere Untersuchungen durchzuführen. Neben dem palliativen Charakter der Radioembolisation könnte so eine Nutzung des Therapieverfahrens in kurativen Konzepten wie der erweiterten Hepatektomie nach Hypertrophieinduktion des verbleibenden Leberlappens erfolgen. Um ein ausreichendes Restlebervolumen nach einer Majorresektion zu erhalten, wird in vielen Fällen mit initial zu geringem Restlebervolumen die Pfortaderembolisation (PVE) genutzt, um die notwendige Hypertrophie der zukünftigen Restleber bzw. „future liver remnant“ (FLR) zu induzieren [118]. Um das Potenzial der Pfortaderembolisation mit der Y90-Radioembolisation zu vergleichen, erfolgte eine Matched-Pair-Analyse (**Veröffentlichung 3**). In dieser wurden die eigenen Daten von 35 Patienten nach Y90-Radioembolisation mit den Daten von 141 Patienten nach Pfortaderembolisation der Arbeitsgruppe von de Baere et al. verglichen [119]. Um eine Vergleichbarkeit der zwei Kohorten herzustellen, mussten klinisch adäquate Match-Kriterien gefunden werden, da die Pfortaderembolisation nur bei potentiell resektablen Lebermetastasen Anwendung findet und somit zu einem deutlich früheren Erkrankungszeitpunkt mit geringerer chemotherapeutischer Vorbelastung eingesetzt wird. Die Daten zur Y90-Radioembolisation stammen wiederum von Patienten, die zuvor mehrere, intensive Chemotherapieregime durchlaufen haben und häufig bei fortgeschrittener Metastasierung am Ende der systemischen Therapieoptionen standen. Als Kriterien wurden (i) ein Restlebervolumen (FLR) ≥ 25% bzw. <25%, (ii) eine Vorbehandlung mit platinhaltiger Chemotherapie, (iii) eine Thrombozytenzahl von ≥200Gpt/l bzw.

<200Gpt/l sowie (iv) der Einschluss des Lebersegments 4 bei der Embolisation definiert. Rationale dieser Match-Kriterien waren (i) der stärkere Volumenzuwachs bei Patienten mit kleinem FLR in der Gruppe von de Baere et al., (ii) die Auslösbarkeit eines sinusoidalen Obstruktionssyndroms (SOS) durch platinhaltige Chemotherapie, (iii) der Einfluß der Thrombozyten bzw. der Plättchen-wachstumsfaktoren auf die Leberregeneration sowie (iv) die verbesserte Hypertrophieinduktion durch Beachtung des Lebersegments 4 [119-123]. In der finalen Matched-Pair-Analyse konnten 26 vollständige Paare eingeschlossen werden. Als primärer Endpunkt betrug der prozentuale Volumenzuwachs des verbleibenden bzw. unbehandelten Leberlappens nach Pfortaderembolisation (PVE) 61,5% und nach Y90-Radioembolisation lediglich 29%, wobei dieser Unterschied statistisch hoch signifikant war (p<0,001). Dieser klare Unterschied unterstreicht zunächst die herausragende Bedeutung der Pfortaderembolisation für die Hypertrophieinduktion vor chirurgischer Majorresektion. Betrachtet man jedoch die Häufigkeit eines Tumorprogresses nach PVE, der mit 6,4 - 33% angegeben wird und durch die Pfortaderembolisation erst stimuliert werden könnte, so lohnt die Betrachtung alternativer Verfahren [124-126]. Die Radioembolisation bietet in diesem Kontext als einziges Verfahren auch eine gleichzeitige Therapie der hepatischen Tumore, wodurch in der **Veröffentlichung 3** in der Subgruppe mit Y90-Radioembolisation ein objektives Ansprechen bzw. eine Stabilität der hepatischen Tumore in 96% der Patienten erreicht werden konnte.

3.3.3 Medikamentöse Prävention der Leberfunktionseinschränkung

Eine wesentliche Reduktion der Leberfunktionseinschränkung nach Y90-Radioembolisation von Lebertumoren (REILD) konnte bereits durch eine zeitlich versetzte Behandlung der beiden Leberlappen erreicht werden (**Veröffentlichung 1**). Ein weiterer Aspekt zur Verbesserung der Verträglichkeit stellt die Untersuchung protektiver Medikamente dar. Da die Häufigkeit einer klinisch signifikanten REILD bereits durch den sequenziellen Therapieansatz gering ist und somit statistische Auswertungen erschwert, bietet sich alternativ die Leberfunktionseinschränkung nach interstitieller Brachytherapie (iBT) der Leber als Surrogatparameter an. Die strahlenphysikalische Dosisdistribution der Brachytherapie mit klar determinierten Isodosen führt in der Magnetresonanztomographie (MRT) der Leber mit dem hepatozytenspezifischen Kontrastmittel Gd-EOB-DTPA zu einer umschriebenen

Minderanreicherung des Leberparenchyms in der Umgebung einer behandelten Leberläsion. Durch Bildfusion der Bestrahlungsplanung und des posttherapeutischen MRT kann die korrespondierende Isodose des umgrenzten Strahlenschadens exakt bestimmt werden [84,127]. Das hepatobiliäre MRT-Kontrastmittel Gd-EOB-DTPA wird ähnlich dem Bilirubin in gesunden Hepatozyten über das organische Anionentransporterprotein 1 (OATP-1) aufgenommen, akkumuliert und zeitverzögert biliär sezerniert. Morphologische Veränderungen in der hepatobiliären Kontrastmittelphase im MRT der Leber wurden darüber hinaus sowohl für die REILD selbst als auch infolge des histopathologisch identischen sinusoidalen Obstruktionssyndroms (SOS) nach Therapie mit Oxaliplatin beschrieben [128,129]. Dies zusammen unterstützt die These, dass der radiogene Funktionsausfall im hepatozytenspezifischen MRT nach interstitieller Brachytherapie als Modell für die radiogene Leberfunktionseinschränkung im Allgemeinen dienen kann. Ausgehend von dieser These wurde eine prospektiv-randomisierte Studie initiiert, die potentiell protektive Medikamente untersucht (**Veröffentlichung 5**). Zur Auswahl kamen Substanzen, die bereits bei der veno-okklusiven Erkrankung (VOD) bzw. beim sinusoidalen Obstruktionssyndrom (SOS) infolge einer Konditionierungsbehandlung zur Stammzelltransplantation untersucht wurden:

(i) Ursodeoxycholsäure (250 mg oral / 3x täglich)[130,131]

(ii) Pentoxifyllin (400 mg oral / 3x täglich)[132,133]

(iii) Enoxaparin (40 mg subkutan / 1x täglich)[134,135].

Die Applikation erfolgte über 8 Wochen, dem typischen Zeitraum der Entwicklung einer RILD bzw. REILD, Nachuntersuchungen erfolgten mittels MRT der Leber jeweils nach sechs Wochen und drei Monaten [83,84,103]. Als primärer Endpunkt wurde die Isodose des Strahlenschadens in der posttherapeutischen MRT der Leber nach 6 Wochen gewählt. Eine Kombination der Präparate führte schließlich zu einer signifikanten Erhöhung der Strahlenresistenz der Leber nach 6 Wochen ausgedrückt als höhere Isodose des Strahlenschadens: 19,1 Gy (Medikamentengruppe) vs. 14,6 Gy (Kontrollgruppe). Das generelle Auftreten eines morphologisch sichtbaren Strahlenschadens war 6 Wochen nach Therapie ebenfalls in der Medikamentengruppe signifikant seltener (45,5%) als in der Kontrollgruppe (90,9%). Ergänzend fand sich jedoch eine Angleichung der Medikamentengruppe an die Kontrollgruppe nach 3 Monaten, indem nun auch hier zu 90,9% eine sichtbare radiogene Dysfunktion des Leberparenchyms um die behandelten Tumore nach

interstitieller Brachytherapie auftrat. Entsprechend ist zu diskutieren, dass die kombinierte Prophylaxe durch die drei Prüfpräparate hinsichtlich der Entwicklung einer fokalen RILD nach Brachytherapie wirksam ist, der Applikationszeitraum von 8 Wochen jedoch nicht den gesamten Zeitraum der Pathogenese abzudecken scheint. In der Literatur sind noch geringere Zeitabstände für die Entwicklung einer VOD nach Stammzelltransplantation von lediglich einigen Tagen bis hin zu einem Monat beschrieben, was sich jedoch durch die stärker hepatotoxischen Regime bei der Konditionierung zur Stammzelltransplantation erklären lässt. Da diese Annahmen offensichtlich nicht für die radiogen ausgelöste VOD in Form der RILD bzw. REILD mit ihrer klinisch meist milderen Ausprägung gelten, müssen weitere Untersuchungen zur Feststellung des tatsächlichen Zeitverlaufs der Erkrankung durchgeführt werden. Entsprechend wurde in einer nachfolgenden Studie das Regime hinsichtlich der zeitlichen Anwendung und Zusammensetzung modifiziert, um weitere Erkenntnisse über den Nutzen einer protektiven Medikation sowohl bei der interstitiellen Brachytherapie als auch letztlich der Y90-Radioembolisation zu gewinnen. Die Daten sind zum Zeitpunkt dieser Abhandlung ausstehend.

4. Anwendung der interventionellen Onkologie bei ausgewählten Entitäten

Die im folgenden Kapitel 4 behandelten Veröffentlichungen sind zur besseren Übersicht im **Anhang** in Tabelle 6 zusammengefasst.

4.1 Kolorektales Karzinom

Das kolorektale Karzinom ist der dritthäufigste Tumor mit geschätzten 1,36 Millionen Neuerkrankungen weltweit pro Jahr - fast jede zehnte Krebserkrankung (9,7%) ist ein kolorektales Karzinom[136]. Für die Tumorstadien UICC I bis III ist die chirurgische Therapie der Goldstandard und wird bei fortgeschrittenem Lokalbefund (T3/4) oder regionalen Lymphknotenmetastasen (N1/2) um eine neoadjuvante und/oder adjuvante Therapie ergänzt [137]. Für lokal begrenzte Metastasen stellt ebenso die Resektion das Standardverfahren dar, sofern diese aufgrund ihrer Lage als resektabel eingestuft werden und der Patient klinisch für eine Operation in Frage kommt. Für Grenzfälle kommt auch ein Downstaging mittels Chemotherapie in Frage, um eine Resektabilität der Metastasen zu erreichen. Der zeitliche Ablauf von Resektion und Chemotherapie wird hier zunehmend an die individuelle Erkrankungssituation angepasst und basiert auf der anzunehmenden Tumorbiologie und Komplexität der Operation [7]. Für hochselektierte Patienten können so durch wiederholte Resektionen beim oligometastasierten kolorektalen Karzinom 5-Jahres-Überlebensraten bis zu 73% erreicht werden [138]. Eine zunehmende Bedeutung als alternative oder additive Methoden erlangen die interventionell-radiologischen Verfahren zur Metastasenbehandlung (**Veröffentlichung 2**). Im Folgenden werden die häufig eingesetzten Therapiemodalitäten bei kolorektalen Metastasen thematisiert sowie andererseits Patientenselektion und Prognosevorhersage im Kontext der Multimodalität diskutiert.

Der Einsatz lokal-ablativer Therapien (RFA, MWA, iBT) ist im Krankheitsverlauf eines metastasierten, kolorektalen Karzinoms in drei Situationen denkbar:

(i) Im Falle resektabler Metastasen, die jedoch aufgrund des Allgemeinzustandes und der Komorbidität des Patienten nicht für eine Operation zugänglich sind. An dieser Stelle ist es chirurgieanalog zu aktuellen Leitlinien (ESMO 2016) denkbar, dass eine lokal-ablative Behandlung ohne bzw. vor einer Erstlinienchemotherapie durchgeführt wird [139].

(ii) Bei den meisten anderen Fällen mit irresektablen Metastasen wird zunächst eine palliative Chemotherapie angezeigt sein, der bei günstigem Ausgang eine lokale Therapie folgen kann bzw. additiv durchgeführt wird [7].

(iii) Wenn im weiteren Krankheitsverlauf durch Toxizität oder Refraktärität keine systemischen Therapieoptionen mehr zur Verfügung stehen, können lokal-ablative Therapien und besonders bei leberdominanter Metastasierung die lokoregionäre Y90-Radioembolisation eine weitere Verlängerung des Überlebens gegenüber best supportive care (BSC) ermöglichen [42].

Bei einzelnen, nicht resektablen Lungen- und Lebermetastasen ist mit der Radiofrequenzablation in der Literatur ein medianes Überleben von 24 bis 36 Monaten erreichbar [140-142]. In der randomisierten CLOCC-Studie wurden mit der Radiofrequenzablation und systemischer Erstlinientherapie sogar 45,6 Monate Gesamtüberleben und ein Vorteil gegenüber der Erstlinientherapie allein gezeigt [13,14]. Im eigenen Patientenkollektiv lag das mediane Gesamtüberleben bei 24,3 bis 26,7 Monaten im unteren Bereich, wobei viele Daten in der Literatur aus chirurgischen Kollektiven mit laparoskopischer RFA entstammen und einer anderen Patientenselektion unterliegen dürften (**Veröffentlichung 11**).
Bei einzelner oder wiederholter Anwendung der interstitiellen Brachytherapie für Oligometastasen ohne Zugänglichkeit für eine RFA aufgrund von Größe oder Lokalisation betrug das mediane Überleben 16,4 bis 19,1 Monate. Dieses deckt sich mit Daten anderer Arbeitsgruppen (18 Monate) und ist aufgrund der fortgeschritteneren Lebertumore (>4cm) erklärbar niedriger gegenüber den Ergebnisse nach thermischen Ablationsverfahren [143]. Für isolierte Lungenmetastasen war wiederum ein medianes Gesamtüberleben von 29,6 Monaten aufzuzeigen und verdeutlicht das Potenzial des Verfahrens der interstitiellen Brachytherapie zur lokalen Tumorablation (**Veröffentlichung 11**).
Wenn man in Betracht zieht, dass diese Patienten aufgrund des Alters oder Komorbiditäten - wie häufig auch im klinischen Alltag zu sehen - nicht für intensive Polychemotherapien oder chirurgische Verfahren zugänglich waren (z.B. Komorbidität bei 62% im Kollektiv), erscheinen die Überlebenszeiten für die eigene Kohorte vorteilhaft [144,145]. Herauszustellen ist, dass schwere Komorbiditäten anhand des Charlson Comorbidity Index (CCI) sowie ein hohes Alter >70 Jahre häufiger als bei durchschnittlichen Kohorten waren, jedoch keinen statistischen

Einfluss auf das Überleben hatten[146]. Somit stellen interventionelle Ablationstechniken einerseits eine wertvolle Alternative zur lokalen Metastasenbehandlung dar, wenn eine chirurgische Therapie aufgrund des Allgemeinzustandes nicht mehr möglich ist. Dies deckt sich mit der Literatur zur systemischen Therapie, die bei hohem Alter und Charlson Comorbidity Index kein Überlebensnachteil aufweist, während die Ergebnisse nicht nur im eigenen Kollektiv sogar auf eine vorteilhafte Tumorbiologie im Alter hinweisen [147-149]. Da sich die Patienten zum Großteil innerhalb der Zweit- oder Drittlinientherapie befanden, ist gegenüber den Literaturdaten mit alleiniger Chemotherapie andererseits auch ein positiver Effekt durch die Addition der Lokalverfahren bezogen auf die jeweilige Therapielinie anzunehmen [150-152]: 22,0 Monate vs. 14,4-20,1 Monate in der Zweitlinie und 17,5 Monate vs. 9,2-15,7 Monate in der Drittlinie.
Eine deutlich schlechtere Prognose weisen Patienten auf, die einen leberdominanten Tumorbefall über die Oligometastasierung hinaus erleiden. In einer Gruppe des beschriebenen Patientenkollektivs (**Veröffentlichung 11**) wurden chemorefraktäre Patienten mit leberdominanter, kolorektaler Metastasierung durch eine Y90-Radioembolisation behandelt und statistische Prognosefaktoren gesucht (**Veröffentlichung 7**). Das mediane Überleben dieser Patienten betrug zunächst nur 6,7 Monate und war damit vergleichbar mit BSC [153]. In einer multivariaten Regressionsanalyse zeigten sich der Allgemeinzustand anhand des Karnofsky Index, die hepatische Tumorlast sowie die Tumormarker CEA/CA19-9 als unabhängige Prognosefaktoren. Anhand der Mediane dieser Parameter konnte ein klinisch anwendbarer Score geschaffen werden, der eine deutliche Abstufung der zu erwartenden Überlebenszeit nach Y90-Radioembolisation ermöglicht:
eine Tumorlast >20%, CEA >130ng/l und/oder CA19-9 >200U/l sowie ein Karnofsky-Index < 80% stehen als gleichberechtigte, negative Prädiktoren für ein medianes Überleben von 4,0 Monaten während das Fehlen aller dieser Faktoren mit einem medianen Gesamtüberleben von 13,4 Monaten verknüpft ist. Liegt nur ein negativer Faktor vor, beträgt das Überleben noch 8,3 Monate und liegt noch sicher über den o.g. Literaturwerten für BSC. Somit kann bei Patienten mit keinem oder nur einem negativen Prädiktor (Score 0/1) der Nutzen einer Y90-Radioembolisation sicher angenommen und im klinischen Alltag empfohlen werden. Für die übrigen Patienten (Score 2/3) besteht ein Überleben von median 5,1 Monaten bei vollständigem Fehlen von Langzeitüberlebenden >12 Monate. Nur die wenigsten Argumente können hier

noch die Durchführung der Y90-RE stützen und für solche Patienten sollten eher Studien für neue Systemtherapien im Fokus stehen.
Wenn es bei den positiv selektierten Fällen nach initialem Ansprechen auf die Radioembolisation zu einem Progress in einem vertretbar langen Zeitraum kommt, kann davon ausgegangen werden, dass prinzipiell radiosensitive Metastasen vorliegen. Obwohl die Radioembolisation konzeptionell ein einmalig anzuwendendes Verfahren darstellt, ist bei einer erneuten Disseminierung von Lebermetastasen im Intervall denkbar, die Behandlung zu wiederholen (**Veröffentlichung 4**). Auch wenn sich die hier gemachten Erfahrungen nur auf Einzelfälle innerhalb weniger Tumorentitäten beschränken, so zeigt sich, dass die Behandlung eines Patienten nach individueller Beurteilung mit mehrfachen Sitzungen einer Y90-Radioembolisation u.a. auch bei kolorektalen Lebermetastasen sicher und effektiv durchführbar ist.
Bisher keine Evidenz konnte für die frühzeitige Anwendung der Y90-Radioembolisation bei der Erstlinientherapie in mehreren, multizentrischen Studien gefunden werden. Die Studienformate SIRFLOX und FOXFIRE fanden keinen Vorteil durch das Hinzufügen der Y90-Radioembolisation zur systemischen Chemotherapie [33,34]. Lediglich für Patienten mit einer prognostisch ungünstigen ras-Mutation zeigte sich eine Tendenz zur Überlebenszeitverlängerung [154]. Damit bleibt die Y90-RE in der Erstlinie auf sehr spezialisierte Konzepte bei hochselektierten Patienten wie zum Erreichen einer kontralateralen Hypertrophie vor Lebermetastasenresektion beschränkt (**Veröffentlichung 3**).
Letztlich muss postuliert werden, dass die besten Ergebnisse aller lokalen Therapieverfahren – ob nun chirurgisch oder interventionell-radiologisch – bei biologisch ohnehin günstigen Tumorerkrankungen erreicht werden und sich nur bei solchen Patienten auch eine signifikante Prognoseverbesserung einstellt. Egal mit welchem lokalen Verfahren therapiert wird - bei echter Oligometastasierung werden im Gegensatz zur Polymetastasierung die Langzeitergebnisse immer besser sein. Die Wertung von Studienergebnissen hängt also stark davon ab, ob durch günstige Ein- und Ausschlusskriterien Polymetastasierungen, die im „Frühstadium“ wie eine Oligometastasierung imponieren, ausgeschlossen werden konnten (siehe auch **Kapitel 2**, Abschnitt 2.2) [8,9,11,12].
Eine entsprechende Wichtigkeit haben damit prognostische Faktoren, wie sie u.a. in den vorgestellten Arbeiten (**Veröffentlichung 7,8**) zu finden sind.

4.2 Nierenzellkarzinom

Das Nierenzellkarzinom ist eine Tumorerkrankung mit steigender Häufigkeit in der weltweiten Bevölkerung und wird durch den Einsatz moderner Bildgebungsverfahren im Frühstadium meist zufällig entdeckt [155].

Bei der Niere besteht der Sonderfall, dass beim Vorliegen einer soliden Raumforderung in der Bildgebung bereits von einem Nierenzellkarzinom ausgegangen werden muss, da benigne Tumore nur in etwa 20% aller Fälle vorliegen und beim Ausschluss radiologisch eindeutiger Angiomyolipome diese Häufigkeit sogar nur 11% beträgt [156]. Entsprechend besteht nach den Leitlinien der deutschen Krebsgesellschaft (AWMF 2017; Nr. 043/017OL) bereits aufgrund des Bildbefundes eine Indikation zur operativen Therapie. Die zunehmende Verfügbarkeit minimal-invasiver Therapieverfahren sowie neue Konzepte wie der aktiven Überwachung (active surveillance) führen jedoch mittlerweile zu Empfehlungen, wonach kleine Nierentumore zunächst mittels Biopsie histologisch gesichert werden sollten, wenn eine therapeutische Strategieänderung zu erwarten ist [157]. Mit einer Größe über 3 cm steigt wiederum die Wachstumsrate und Metastasierungshäufigkeit exponentiell an [158]. Obwohl lokal begrenzte Nierentumore technisch immer operabel sind, können Alter und Komorbiditäten das operative Outcome negativ beeinflussen und zeigen damit den Bedarf an Behandlungsalternativen auf [159]. Zu den etablierten Verfahren bei der interventionellen Behandlung kleiner Nierentumore bzw. Nierenzellkarzinome (T1a; < 4cm) zählen die Radiofrequenzablation (RFA), Mikrowellenablation (MWA) und Kryoablation (CA) (**Veröffentlichung 17**). Während die Ergebnisse im Stadium T1a mit denen der partiellen Nephrektomie vergleichbar sind, sinkt die Erfolgsrate der thermischen Ablationsverfahren bei größeren Tumoren (T1b, >4cm) aufgrund der technischen Limitationen [78,160]. Für ältere und komorbide Patienten besteht folglich ein großer Bedarf an minimal-invasiven bzw. interventionellen Alternativen zur klassisch-chirurgischen Therapie. Wichtig in diesem Patientenkollektiv ist jedoch die Verträglichkeit der Therapie, bei der u.a. eine Dialysepflicht infolge der Behandlung streng vermieden werden sollte. In einer Phase-I-Studie konnte für die CT-geführte, interstitielle Brachytherapie bei lokal begrenzten als auch lokal fortgeschrittenen Nierenmalignomen ein geringes und damit günstiges Nebenwirkungs- und Komplikationsprofil gezeigt werden(**Veröffentlichung 20**). Wichtig ist in kommenden Phase-II-Studien, den potentiellen Vorteil gegenüber den thermoablativen Verfahren aufzuzeigen, der sich

weitgehend durch die technischen Grenzen der RFA, MWA und CA definiert - beim Stadium T1b und bei der Lokalisation im Nierenbecken.
Die Daten für die lokale Kontrolle sind hier auch vergleichbar zu den Ergebnissen nach einer stereotaktischen Präzisionsbestrahlung (SBRT) von Nierenzellkarzinomen, bei der kurzfristige, lokale Kontrollraten bis 100% erreichen werden können und nur eine moderate Absenkung der glomerulären Nierenfunktion zu beobachten ist [161-163]. Schwierig in der Beurteilung dieser kurzfristigen Ergebnisse der SBRT als auch iBT bleibt die langsame Wachstumsrate kleiner Nierenzellkarzinome, die lange Nachbeobachtungszeiträume benötigen um etwaige Rezidive überhaupt detektieren zu können [164].
Die interstitielle Brachytherapie kann weiterhin auch beim hepatisch metastasierten Nierenzellkarzinom eingesetzt werden (**Veröffentlichung 18**). Bei 14 Patienten wurden 54 Metastasen mit einem mittleren Durchmesser von 2,9 cm und einem maximalen Durchmesser bis über 10 cm behandelt. Selbst bei dieser Größendimension, die teils einer thermischen Ablation technisch nicht zugänglich gewesen wäre, konnte eine lokale Kontrollrate von 92,6% erreicht werden. Vergleichbare Daten liegen für die Radiofrequenz- und Mikrowellenablation in der Literatur nicht vor – für die stereotaktische Bestrahlung (SBRT) sind ähnlich kleine Kollektive publiziert und weisen eine lokale Kontrollrate von 90,2% auf [165]. Der genaue Stellenwert lokaler Therapieverfahrung beim oligometastasierten Nierenzellkarzinom muss daher noch weiter in Hinblick auf Überleben und Lebensqualität untersucht werden.

4.3 Hepatozelluläres Karzinom

Das hepatozelluläre Karzinom (HCC) stellt den häufigsten, lebereigenen Krebs dar und weist weltweit eine steigende Inzidenz auf - Ursache ist hierfür die Entstehung aus zunehmenden Leberparenchymerkrankungen, insbesondere der chronischen Virushepatitis und Leberzirrhose [166]. Für das HCC sind die Radiofrequenzablation (RFA) und transarterielle Chemoembolisation (TACE) schon länger etablierte Therapieverfahren und in der BCLC-Klassifikation für die Stadien 0/A (RFA) bzw. B (TACE) empfohlen [46]. Der BCLC-Therapiealgorithmus fasst für die klinische Entscheidungsfindung gut die Tumorausdehnung, die in der Zirrhose immanent wichtige Leberfunktion und den Allgemeinzustand des Patienten in Patientengruppen zusammen. Die Gruppeneinteilungen basieren jedoch weitgehend auf den zum Zeitpunkt der Erstellung verfügbaren Therapiemöglichkeiten des hepatozellulären Karzinoms. Insbesondere das Stadium BCLC B spannt sich von einer Leberfunktion mit 5 bis 9 Punkten im Child-Pugh-Score über >3 kleine Herde bis zu einer diffusen, bilobären Tumorausdehnung lediglich ohne Pfortaderinvasion [167]. Entsprechend wurde eine Subklassifikation vorgeschlagen, die Patientengruppen mit einem Gesamtüberleben von 28,5 Monaten (B1) bis 5,9 Monaten (B4) auftrennt und damit zu einer besseren Patientenselektion insbesondere bei der Chemoembolisation beiträgt [44]. Weiterhin scheint in der Subgruppe B2 ein Vorteil für die Y90-Radioembolisation gegenüber der Chemoembolisation zu bestehen [51].

Neben der Radiofrequenzablation haben sich auch weitere Ablationstechniken wie die interstitielle Brachytherapie entwickelt, die zusammen mit besseren Selektionskriterien für die Chirurgie das therapeutische Spektrum für Patienten im Stadium BCLC 0/A als auch BCLC B stark erweitert haben[74]. So kamen in einer eigenen Kohorte die Chemoembolisation (TACE) und interstitielle Brachytherapie (iBT) nach multidisziplinärer Entscheidung auch in den Stadien BCLC A bis C zur Anwendung (**Veröffentlichung 15**). Über alle Stadien hinweg konnte nach Randomisierung für TACE vs. iBT ein Gesamtüberleben von etwa 24 vs. 29 Monaten verzeichnet werden. Der Unterschied zwischen den Gruppen war nicht signifikant (p=0,097), jedoch erfolgte bei fast einem Drittel der Patienten mit TACE ein Cross-over zur interstitiellen Brachytherapie. Für lokale und lokoregionäre Therapieverfahren ist es von zusätzlicher Wichtigkeit, dass lokal begrenzte Progressionen erneut lokal behandelt werden können. In diesem Hinblick konnte die

interstielle Brachytherapie das Überleben bis zum unbehandelbaren Progress bzw. Cross-over signifikant verlängern (p=0,021), was sich am besten durch Tumore mit komplexem arteriellen Zugang zum Gefäßbett bei der TACE erklären lässt [75-77]. Dies kann auch eine der Ursachen sein, dass bisher keine eindeutige, klinische Evidenz für die Wirksamkeit der transarterielle Y90-Radioembolisation in großen Patientenkollektiven gefunden werden konnte, da die technische Durchführbarkeit der Radioembolisation kein eindeutiges Eingangskriterium in den Studien war [49,50]. Abzuwarten bleiben auch mögliche multimodale Therapieansätze mit Einbindung der zahlreichen, neuen Systemtherapien, die neben dem lange Zeit einzigen effektiven Proteinkinaseinhibitor Sorafenib kürzlich für das fortgeschrittene HCC zugelassen wurden [168-171]. Denkbar wäre einerseits der Einsatz als Adjuvanz nach kurativer Resektion bzw. Ablation eines HCC wie dies bereits für Sorafenib mit negativem Ergebnis untersucht wurde [172]. Auch die Kombination aus systemischer Sorafenibgabe mit TACE brachte bisher keinen Durchbruch, wohingegen die intraarterielle Anwendung von Sorafenib im VX2-Tiermodell vielversprechende Ergebnisse aufweist [173,174]. Bei allen methodischen Neuerungen sollte aber nicht vergessen werden, dass die personalisierte Anwendung aller bereits vorhandenen Therapieverfahren einen Vorteil für den Patienten ausmachen kann [175,176].

4.4 Ösophaguskarzinom

Obwohl das Ösophaguskarzinom weltweit an achter Stelle der Tumorinzidenz steht, stellt es die sechst häufigste, krebsbedingte Todesursache dar [136]. Von den zwei histologischen Subtypen tritt hierbei das Plattenepithelkarzinom deutlich häufiger auf als das überwiegend auf einem Barrett-Syndrom basierende Adenokarzinom [177]. Auch wenn die meisten Patienten initial eine kurative Therapie durchlaufen, entwickelt etwa die Hälfe im Verlauf ein Rezidiv oder eine Metastasierung, die aufgrund der geringen Therapieoptionen mit einem deutlich eingeschränkten Gesamtüberleben von 3 bis 7 Monaten assoziiert ist [178-180]. Ursache hierfür sind unter anderem die limitierten Optionen für eine systemische Chemotherapie insbesondere beim Subtyp des Plattenepithelkarzinoms [181]. Wenn eine Oligometastasierung vorliegt, kann eine lokale Therapie wie die Radiofrequenzablation oder interstitielle Brachytherapie zur Tumorkontrolle beitragen und potentiell das Überleben der Patienten verlängern. Zur Evaluierung des Stellenwertes der interstitiellen Brachytherapie wurden in einer Studie 11 Patienten mit 21 nicht resektablen Metastasen untersucht (**Veröffentlichung 14**). Bei 14 viszeralen Metastasen und 7 Lungenmetastasen mit einem mittleren Durchmesser von 2,2 cm lag die lokale Kontrollrate bei 85,7%. Neben den behandelten Metastasen zeigte sich häufig ein weiterer Progress der Metastasierung, das progressionsfreie Überleben lag daher bei nur 3,4 Monaten. Insgesamt konnte ein medianes Gesamtüberleben von 13,7 Monaten erreicht werden. Zum Vergleich können nur wenige Studien mit ebenso kleinen Patientenkollektiven herangezogen werden. Für die Resektion von Metastasen eines Ösophaguskarzinoms sind Überlebensraten von 50% in einem medianen Nachsorgezeitraum von 22 Monaten beschrieben [182]. Bei prognostisch gegenüber viszeralen Metastasen meist günstigeren Lungenmetastasen sind für die Radiofrequenzablation lokale Kontrollraten von 74,2% bzw. 83,0% bei einem 1-Jahres-Überleben von 85,7% bzw. 77,8% beschrieben [183,184]. Folglich zeigt die interstitielle Brachytherapie ähnliche Kontrollraten wie die Radiofrequenzablation und kann als ergänzendes Verfahren zur lokalen Kontrolle von Metastasen des Ösophaguskarzinoms eingesetzt werden. Da die Patienten häufig einen kurzfristigen Tumorprogress an anderer Stelle nach der Behandlung zeigen, ist die sorgfältige Patientenselektion und Abschätzung der Tumorbiologie entscheidend und die Therapieindikation sollte auf einem multidisziplinären Konsens basieren.

4.5 Analkarzinom

Das Analkarzinom ist eine seltene Tumorentität, speziell gemessen an der Häufigkeit des kolorektalen Karzinoms [185]. In der Leitlinie der europäischen Fachgesellschaft für Medizinische Onkologie 2016 wird das 5-Jahres-Überleben mit 44 bis 78% angegeben und hängt stark von einer lymphogenen Metastasierung ab [186]. Metastasen außerhalb des Beckens finden sich nur bei 5-8% der Fälle dieser bereits seltenen Entität bei Diagnosestellung. Während beim Primärtumor vor allem der konventionellen Strahlentherapie im Rahmen einer primären Radiochemotherapie eine wesentliche Bedeutung zukommt, spielt die interventionelle Onkologie hier keine Rolle. Im M1-Stadium beträgt die 2-Jahres-Überlebensrate nur 10% und therapeutische Empfehlungen basieren zumeist auf der Resektion lokal begrenzter Metastasen sowie einer systemischen Chemotherapie mit Cisplatin und 5-Fluorouracil. Im Universitätsklinikum Magdeburg wurden bisher 7 Patienten mit Leber-, Lungen- und Lymphknotenmetastasen eines Analkarzinoms interventionell behandelt und nachfolgend publiziert (**Veröffentlichung 10**): nach multidisziplinärer Therapieentscheidung erfolgte die Behandlung bereits chemotherapeutisch vorbehandelter Patienten an insgesamt 38 Metastasen mittels bildgeführter, interstitieller Brachytherapie. Es war eine lokale Tumorkontrollrate von 97,4% zu erreichen und das mediane Gesamtüberleben lag bei 25,2 Monaten. Nach einem weiteren Tumorprogress und erneuter Therapie lag das Überleben noch bei 18,3 Monaten. Bei der multimodalen Behandlung von Metastasen durch ergänzende, chirurgische Resektion und RFA konnte das Überleben in zwei vergleichenden Studien gegenüber Chemotherapie allein um 9 Monate oder sogar 31 Monate verlängert werden [187,188]. Auch wenn in der hiesigen Kohorte eine solche Analyse nicht möglich ist, so kommt der interstitiellen Brachytherapie trotzdem eine Bedeutung als lokalablatives Verfahren bei der Behandlung des metastasierten Analkarzinoms zu. Wie auch bei anderen Tumorentitäten ist die lokale Behandlung durch chirurgische Resektion und thermische Ablation (RFA, MWA) häufig technisch begrenzt und die bildgeführte Brachytherapie könnte die Ergebnisse einer multidisziplinären Behandlung durch Erweiterung des Patientenkollektivs weiter verbessern.

5. Zusammenfassung

Die vorliegende Arbeit und die zugehörigen Publikationen umfassen sowohl technische Weiterentwicklungen als auch klinische Verbesserungen bei Patientenselektion und Indikationsstellung verschiedener Verfahren der interventionellen Onkologie. Der Fokus lag auf den Methoden der bildgeführten, interstitiellen Brachytherapie in der Leber und Niere sowie auf der Y90-Radioembolisation der Leber. Die Einleitung definierte zwei wesentliche Kriterien für die Anwendung der interventionellen Onkologie:
(i) Die technische Durchführbarkeit der Verfahren in Bezug auf Zugangsweg, Komplikationen und Organfunktion bei einer hinreichenden Effektivität sowie
(ii) die onkologische Sinnhaftigkeit einer lokalen bzw. loko-regionären Behandlung bei einer metastasierten Grunderkrankung.
Die vorlegten Daten erlauben die Schlussfolgerung, dass die interstitielle Brachytherapie ein effektives Verfahren zur lokalen Tumorablation darstellt. Während die thermischen Ablationsverfahren (Radiofrequenzablation, Mikrowellenablation) hinsichtlich der Tumorgröße sowie Lokalisation in der Nähe hitzevulnerabler Strukturen technisch limitiert sein können, erlaubt die interstitielle Brachytherapie auch eine Ablation größerer Metastasen und kann in der Nähe von Gallenwegen und großen Gefäßen angewendet werden. Limitation der interstitiellen Brachytherapie kann die Dosisexposition angrenzender Organe wie des Gastrointestinums sein - hier wurde die jeweilige Grenzdosis für die Ausprägung radiogener Komplikationen erarbeitet, wodurch bei strenger Einhaltung typische Folgen einer Bestrahlung verhindert werden können. Um eine etwaige Einschränkung der erforderlichen Dosis zur vollständigen Tumorablation in der Nähe radiosensitiver Organe zu vermeiden, wurde zudem eine neue Interventionstechnik zur Distanzierung der Risikoorgane entwickelt. Weiterhin wurde die Sonographie bei der sonst CT-geführten Katheteranlage eingeführt, wodurch neben einer Verbesserung der Läsions-visualisierung bei der Intervention eine Reduktion der Strahlenexposition des Radiologen erreicht werden kann (Veröffentlichungen 6, 9, 12, 13, 19).
Durch diese technischen Vorteile ließ sich die Bedeutung der interstitiellen Brachytherapie vor allem bei der lokalen Ablation von Organmetastasen häufiger Entitäten wie dem kolorektalen Karzinom oder primärer Lebertumore wie dem hepatozellulären Karzinom darstellen.

Darüber hinaus konnte eine Indikation bei der Ablation des Nierenzellkarzinoms sowie seltenerer Metastasenentitäten wie dem Ösophagus- oder Analkarzinom aufgezeigt werden (Veröffentlichungen 2, 10, 11, 14, 15, 17, 18, 20).
Die Y90-Radioembolisation als loko-regionäres, palliatives Verfahren zur Behandlung primärer und sekundärer Lebertumore konnte in dieser Arbeit vor allem in Hinblick auf die Therapieverträglichkeit verbessert werden. Sowohl durch sequenzielle Applikationstechnik als auch pharmakologische Einflussnahme steht ein besserer Erhalt der Leberfunktion, eine Reduktion klinisch relevanter Nebenwirkungen und damit potentiell auch eine höhere Lebensqualität der Patienten in Aussicht.
Weiterhin wurde die Möglichkeit einer wiederholten Anwendung der sonst einmalig durchgeführten Y90-Radioembolisation untersucht (Veröffentlichungen 1, 4, 5).
Die therapeutische Effektivität wurde vor allem beim hepatisch metastasierten kolorektalen Karzinom analysiert und der Stellenwert bei älteren und komorbiden Patienten herausgearbeitet. Darüber hinaus wurden geeignete Instrumente geschaffen, um die Entscheidungsfindung und bestmögliche Patientenauswahl im onkologischen Alltag zu erleichtern (Veröffentlichungen 2, 7, 8, 11).

Durch die klinische Zentrierung der Publikationen fanden die Ergebnisse dieser Arbeit Eingang in den Behandlungsstandard bzw. die Standardprozeduren der Klinik für Radiologie und Nuklearmedizin am Universitätsklinikum Magdeburg:
(i) Durch die Analyse von Stichkanalmetastasen nach interstitieller Brachytherapie beim hepatozellulären Karzinom wurde die Bestrahlung des Stichkanals eingeführt, wodurch die Weiterentwicklung kurativer Konzepte unterstützt werden kann und eine Risikoabwägung bei der Wahl eines geeigneten Ablationsverfahrens für die Überbrückung zur Lebertransplantation möglich wird (Veröffentlichung 16)
(ii) Die Y90-Radioembolisation der Leber wird nun bis auf selektierte Fälle sequenziell – beide Leberlappen zeitlich versetzt – angewendet, um die Nebenwirkungshäufigkeit signifikant zu senken (Veröffentlichung 1).
(iii) Zur Prävention einer radiogenen Leberfunktionseinschränkung nach Y90-Radioembolisation werden die Medikamente Ursodeoxycholsäure, Enoxaparin sowie Pentoxifyllin in einem definierten posttherapeutischen Zeitraum angewendet (Veröffentlichung 5).

(iv) Vor der Indikationsstellung zur Y90-Radioembolisation des hepatisch metastasierten kolorektalen Karzinoms in der Salvage-Situation wird durch die Generierung eines Scores auf Basis klinischer Parameter regelmäßig eine Prognoseabschätzung durchgeführt (Veröffentlichung 7).

Letztlich wurden die Ergebnisse der Veröffentlichung 3 in der Leitlinie der europäischen Gesellschaft für Medizinische Onkologie (ESMO) für das metastasierte, kolorektale Karzinom im Jahr 2016 zitiert. Hiermit erhält die Y90-Radioembolisation einen Stellenwert als alternatives Verfahren zur Pfortaderembolisation für die Hypertrophieinduktion der (Rest-)Leber vor erweiterter Resektion in speziellen klinischen Situationen.

6. Literatur

1. Smith KA, Kim HS. Interventional radiology and image-guided medicine: interventional oncology. Semin Oncol 2011; 38: 151-162
2. Adam A, Kenny LM. Interventional oncology in multidisciplinary cancer treatment in the 21(st) century. Nat Rev Clin Oncol 2015; 12: 105-113
3. Liapi E, Geschwind JF. Transcatheter and ablative therapeutic approaches for solid malignancies. J Clin Oncol 2007; 25: 978-986
4. Liehr UB, Wendler JJ, Blaschke S et al. [Irreversible electroporation: the new generation of local ablation techniques for renal cell carcinoma]. Urologe A 2012; 51: 1728-1734
5. Nielsen K, Scheffer HJ, Vieveen JM et al. Anaesthetic management during open and percutaneous irreversible electroporation. Br J Anaesth 2014; 113: 985-992
6. Jones SN. Interventional radiology in a palliative care setting. Palliat Med 1995; 9: 319-326
7. Van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016; 27: 1386-1422
8. deSouza NM, Tempany CM. A risk-based approach to identifying oligometastatic disease on imaging. Int J Cancer 2019; 144: 422-430
9. Uppal A, Ferguson MK, Posner MC et al. Towards a molecular basis of oligometastatic disease: potential role of micro-RNAs. Clin Exp Metastasis 2014; 31: 735-748
10. Withers HR, Lee SP. Modeling growth kinetics and statistical distribution of oligometastases. Semin Radiat Oncol 2006; 16: 111-119
11. Lussier YA, Xing HR, Salama JK et al. MicroRNA expression characterizes oligometastasis(es). PLoS One 2011; 6: e28650
12. Pitroda SP, Khodarev NN, Huang L et al. Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. Nat Commun 2018; 9: 1793
13. Ruers T, Punt C, Van Coevorden F et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-

resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 2012; 23: 2619-2626

14. Ruers T, Van Coevorden F, Punt CJ et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. J Natl Cancer Inst 2017; 109:
15. Carrato A, Abad A, Massuti B et al. First-line panitumumab plus FOLFOX4 or FOLFIRI in colorectal cancer with multiple or unresectable liver metastases: A randomised, phase II trial (PLANET-TTD). Eur J Cancer 2017; 81: 191-202
16. Heinemann V, von Weikersthal LF, Decker T et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014; 15: 1065-1075
17. Yamazaki K, Nagase M, Tamagawa H et al. Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G). Ann Oncol 2016; 27: 1539-1546
18. Aprile G, Fontanella C, Bonotto M et al. Timing and extent of response in colorectal cancer: critical review of current data and implication for future trials. Oncotarget 2015; 6: 28716-28730
19. Nozawa H, Nishikawa T, Tanaka T et al. 'Deepness of Response' Is Associated with Overall Survival in Standard Systemic Chemotherapy for Metastatic Colorectal Cancer. Chemotherapy 2014; 60: 360-367
20. Berenbaum MC. In vivo determination of the fractional kill of human tumor cells by chemotherapeutic agents. Cancer Chemother Rep 1972; 56: 563-571
21. De Lerma Barbaro A. The complex liaison between cachexia and tumor burden (Review). Oncol Rep 2015; 34: 1635-1649
22. Lucia S, Esposito M, Rossi Fanelli F et al. Cancer cachexia: from molecular mechanisms to patient's care. Crit Rev Oncog 2012; 17: 315-321
23. Stephens NA, Skipworth RJ, Fearon KC. Cachexia, survival and the acute phase response. Curr Opin Support Palliat Care 2008; 2: 267-274
24. Collettini F, Schnapauff D, Poellinger A et al. Hepatocellular carcinoma: computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of large (5-7 cm) and very large (>7 cm) tumours. Eur Radiol 2012; 22: 1101-1109

25. Miyake H, Miyazaki A, Imai S et al. Early Tumor Shrinkage Under Treatment with First-line Tyrosine Kinase Inhibitors as a Predictor of Overall Survival in Patients with Metastatic Renal Cell Carcinoma: a Retrospective Multi-Institutional Study in Japan. Target Oncol 2016; 11: 175-182
26. Osumi H, Takahari D, Shinozaki E et al. Associations between early tumor shrinkage and depth of response and clinical outcomes in patients treated with 1st-line chemotherapy for advanced gastric cancer. Gastric Cancer 2018; 21: 267-275
27. Lin ZY, Li GL, Chen J et al. Effect of heat sink on the recurrence of small malignant hepatic tumors after radiofrequency ablation. J Cancer Res Ther 2016; 12: C153-C158
28. Vigano L, Laurenzi A, Solbiati L et al. Open Liver Resection, Laparoscopic Liver Resection, and Percutaneous Thermal Ablation for Patients with Solitary Small Hepatocellular Carcinoma (</=30 mm): Review of the Literature and Proposal for a Therapeutic Strategy. Dig Surg 2018; 35: 359-371
29. Wang LJ, Zhang ZY, Yan XL et al. Radiofrequency ablation versus resection for technically resectable colorectal liver metastasis: a propensity score analysis. World J Surg Oncol 2018; 16: 207
30. Mulier S, Ruers T, Jamart J et al. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? An update. Dig Surg 2008; 25: 445-460
31. van Amerongen MJ, Jenniskens SFM, van den Boezem PB et al. Radiofrequency ablation compared to surgical resection for curative treatment of patients with colorectal liver metastases - a meta-analysis. HPB (Oxford) 2017; 19: 749-756
32. Meijerink MR, Puijk RS, van Tilborg A et al. Radiofrequency and Microwave Ablation Compared to Systemic Chemotherapy and to Partial Hepatectomy in the Treatment of Colorectal Liver Metastases: A Systematic Review and Meta-Analysis. Cardiovasc Intervent Radiol 2018; 41: 1189-1204
33. van Hazel GA, Heinemann V, Sharma NK et al. SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer. J Clin Oncol 2016; 34: 1723-1731

34. Wasan HS, Gibbs P, Sharma NK et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol 2017; 18: 1159-1171
35. Marsala A, Lee EW, Padia SA. Yttrium-90 Radioembolization for Metastatic Colorectal Cancer: Outcomes by Number of Lines of Therapy. Semin Intervent Radiol 2017; 34: 116-120
36. van Hazel GA, Pavlakis N, Goldstein D et al. Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. J Clin Oncol 2009; 27: 4089-4095
37. van Kessel CS, Samim M, Koopman M et al. Radiological heterogeneity in response to chemotherapy is associated with poor survival in patients with colorectal liver metastases. Eur J Cancer 2013; 49: 2486-2493
38. Sebagh M, Allard MA, Bosselut N et al. Evidence of intermetastatic heterogeneity for pathological response and genetic mutations within colorectal liver metastases following preoperative chemotherapy. Oncotarget 2016; 7: 21591-21600
39. Andreou A, Kopetz S, Maru DM et al. Adjuvant chemotherapy with FOLFOX for primary colorectal cancer is associated with increased somatic gene mutations and inferior survival in patients undergoing hepatectomy for metachronous liver metastases. Ann Surg 2012; 256: 642-650
40. Zhao L, Wang J, Li H et al. Meta-analysis comparing maintenance strategies with continuous therapy and complete chemotherapy-free interval strategies in the treatment of metastatic colorectal cancer. Oncotarget 2016; 7: 33418-33428
41. Bester L, Meteling B, Pocock N et al. Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. J Vasc Interv Radiol 2012; 23: 96-105
42. Seidensticker R, Denecke T, Kraus P et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone

for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol 2012; 35: 1066-1073
43. Chan AW, Kumada T, Toyoda H et al. Integration of albumin-bilirubin (ALBI) score into Barcelona Clinic Liver Cancer (BCLC) system for hepatocellular carcinoma. J Gastroenterol Hepatol 2016; 31: 1300-1306
44. Weinmann A, Koch S, Sprinzl M et al. Survival analysis of proposed BCLC-B subgroups in hepatocellular carcinoma patients. Liver Int 2015; 35: 591-600
45. Zhang EL, Liang BY, Chen XP et al. Severity of liver cirrhosis: a key role in the selection of surgical modality for Child-Pugh A hepatocellular carcinoma. World J Surg Oncol 2015; 13: 148
46. Bruix J, Sherman M, Practice Guidelines Committee AAftSoLD. Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208-1236
47. Sangro B, Carpanese L, Cianni R et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology 2011; 54: 868-878
48. Titano J, Noor A, Kim E. Transarterial Chemoembolization and Radioembolization across Barcelona Clinic Liver Cancer Stages. Semin Intervent Radiol 2017; 34: 109-115
49. Chow PKH, Gandhi M, Tan SB et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol 2018; 36: 1913-1921
50. Vilgrain V, Pereira H, Assenat E et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol 2017; 18: 1624-1636
51. Cappelli A, Sangro P, Mosconi C et al. Transarterial radioembolization in patients with hepatocellular carcinoma of intermediate B2 substage. Eur J Nucl Med Mol Imaging 2019; 46: 661-668
52. Pereira PL, Trubenbach J, Schmidt D. [Radiofrequency ablation: basic principles, techniques and challenges]. Rofo 2003; 175: 20-27
53. Anderson EM, Lees WR, Gillams AR. Early indicators of treatment success after percutaneous radiofrequency of pulmonary tumors. Cardiovasc Intervent Radiol 2009; 32: 478-483

54. Wang X, Sofocleous CT, Erinjeri JP et al. Margin size is an independent predictor of local tumor progression after ablation of colon cancer liver metastases. Cardiovasc Intervent Radiol 2013; 36: 166-175
55. Kim KH, Yoon YS, Yu CS et al. Comparative analysis of radiofrequency ablation and surgical resection for colorectal liver metastases. J Korean Surg Soc 2011; 81: 25-34
56. Yamakado K, Inoue Y, Takao M et al. Long-term results of radiofrequency ablation in colorectal lung metastases: single center experience. Oncol Rep 2009; 22: 885-891
57. Vietti Violi N, Duran R, Demartines N et al. Local recurrence rate in patients with colorectal cancer liver metastasis after wedge resection or percutaneous radiofrequency ablation. Int J Hyperthermia 2018; 34: 1020-1028
58. Nanko M, Shimada H, Yamaoka H et al. Micrometastatic colorectal cancer lesions in the liver. Surg Today 1998; 28: 707-713
59. Wakai T, Shirai Y, Sakata J et al. Appraisal of 1 cm hepatectomy margins for intrahepatic micrometastases in patients with colorectal carcinoma liver metastasis. Ann Surg Oncol 2008; 15: 2472-2481
60. Bretschneider T, Ricke J, Gebauer B et al. Image-guided high-dose-rate brachytherapy of malignancies in various inner organs - technique, indications, and perspectives. J Contemp Brachytherapy 2016; 8: 251-261
61. Ricke J, Wust P. Computed tomography-guided brachytherapy for liver cancer. Semin Radiat Oncol 2011; 21: 287-293
62. Collettini F, Singh A, Schnapauff D et al. Computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of metastases adjacent to the liver hilum. Eur J Radiol 2013; 82: e509-514
63. Van den Begin R, Engels B, Gevaert T et al. Impact of inadequate respiratory motion management in SBRT for oligometastatic colorectal cancer. Radiother Oncol 2014; 113: 235-239
64. Schaefer PJ, Schaefer FK, Heller M et al. CT fluoroscopy guided biopsy of small pulmonary and upper abdominal lesions: efficacy with a modified breathing technique. J Vasc Interv Radiol 2007; 18: 1241-1248
65. Gianfelice D, Lepanto L, Perreault P et al. Effect of the learning process on procedure times and radiation exposure for CT fluoroscopy-guided percutaneous biopsy procedures. J Vasc Interv Radiol 2000; 11: 1217-1221

66. Kloeckner R, dos Santos DP, Schneider J et al. Radiation exposure in CT-guided interventions. Eur J Radiol 2013; 82: 2253-2257
67. Wu J, Chen P, Xie YG et al. Comparison of the effectiveness and safety of ultrasound- and CT-guided percutaneous radiofrequency ablation of non-operation hepatocellular carcinoma. Pathol Oncol Res 2015; 21: 637-642
68. Rak M, Konig T, Tonnies KD et al. Joint deformable liver registration and bias field correction for MR-guided HDR brachytherapy. Int J Comput Assist Radiol Surg 2017; 12: 2169-2180
69. Ricke J, Thormann M, Ludewig M et al. MR-guided liver tumor ablation employing open high-field 1.0T MRI for image-guided brachytherapy. Eur Radiol 2010; 20: 1985-1993
70. Chargari C, Van Limbergen E, Mahantshetty U et al. Radiobiology of brachytherapy: The historical view based on linear quadratic model and perspectives for optimization. Cancer Radiother 2018; 22: 312-318
71. Manning MA, Zwicker RD, Arthur DW et al. Biologic treatment planning for high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 2001; 49: 839-845
72. Collettini F, Schreiber N, Schnapauff D et al. CT-guided high-dose-rate brachytherapy of unresectable hepatocellular carcinoma. Strahlenther Onkol 2015; 191: 405-412
73. Mohnike K, Wieners G, Schwartz F et al. Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: safety, efficacy, and effect on survival. Int J Radiat Oncol Biol Phys 2010; 78: 172-179
74. Vogel A, Cervantes A, Chau I et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29: iv238-iv255
75. Bouvier A, Ozenne V, Aube C et al. Transarterial chemoembolisation: effect of selectivity on tolerance, tumour response and survival. Eur Radiol 2011; 21: 1719-1726
76. Hu HT, Kim JH, Lee LS et al. Chemoembolization for hepatocellular carcinoma: multivariate analysis of predicting factors for tumor response and survival in a 362-patient cohort. J Vasc Interv Radiol 2011; 22: 917-923
77. Kim HC, Chung JW, Lee W et al. Recognizing extrahepatic collateral vessels that supply hepatocellular carcinoma to avoid complications of transcatheter arterial chemoembolization. Radiographics 2005; 25 Suppl 1: S25-39

78. Psutka SP, Feldman AS, McDougal WS et al. Long-term oncologic outcomes after radiofrequency ablation for T1 renal cell carcinoma. Eur Urol 2013; 63: 486-492
79. Streitparth F, Pech M, Bohmig M et al. In vivo assessment of the gastric mucosal tolerance dose after single fraction, small volume irradiation of liver malignancies by computed tomography-guided, high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 2006; 65: 1479-1486
80. Liu CH, Yu CY, Chang WC et al. Computed tomographic-guided percutaneous radiofrequency ablation with hydrodissection of hepatic malignancies in the subcapsular location: Evaluation of safety and technical efficacy. J Chin Med Assoc 2016; 79: 93-100
81. Eriguchi T, Takeda A, Sanuki N et al. Acceptable toxicity after stereotactic body radiation therapy for liver tumors adjacent to the central biliary system. Int J Radiat Oncol Biol Phys 2013; 85: 1006-1011
82. Toesca DA, Osmundson EC, Eyben RV et al. Central liver toxicity after SBRT: An expanded analysis and predictive nomogram. Radiother Oncol 2017; 122: 130-136
83. Lawrence TS, Robertson JM, Anscher MS et al. Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 1995; 31: 1237-1248
84. Seidensticker M, Seidensticker R, Mohnike K et al. Quantitative in vivo assessment of radiation injury of the liver using Gd-EOB-DTPA enhanced MRI: tolerance dose of small liver volumes. Radiat Oncol 2011; 6: 40
85. Doi H, Shiomi H, Masai N et al. Threshold doses and prediction of visually apparent liver dysfunction after stereotactic body radiation therapy in cirrhotic and normal livers using magnetic resonance imaging. J Radiat Res 2016; 57: 294-300
86. Stewart FA, Te Poele JA, Van der Wal AF et al. Radiation nephropathy--the link between functional damage and vascular mediated inflammatory and thrombotic changes. Acta Oncol 2001; 40: 952-957
87. Takagi T, Mir MC, Sharma N et al. Compensatory hypertrophy after partial and radical nephrectomy in adults. J Urol 2014; 192: 1612-1618
88. Bertot LC, Sato M, Tateishi R et al. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. Eur Radiol 2011; 21: 2584-2596

89. Stigliano R, Marelli L, Yu D et al. Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC. Cancer Treat Rev 2007; 33: 437-447
90. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018; 69: 182-236
91. Hanna RF, Miloushev VZ, Tang A et al. Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma. Abdom Radiol (NY) 2016; 41: 71-90
92. Lopez KT, Kuwada SK, Wong LL. Consequences of needle tract seeding of hepatocellular cancer after liver transplant. Clin Transplant 2013; 27: E400-406
93. Francica G. Needle track seeding after radiofrequency ablation for hepatocellular carcinoma: prevalence, impact, and management challenge. J Hepatocell Carcinoma 2017; 4: 23-27
94. Shirai K, Tamai H, Shingaki N et al. Clinical features and risk factors of extrahepatic seeding after percutaneous radiofrequency ablation for hepatocellular carcinoma. Hepatol Res 2011; 41: 738-745
95. Denecke T, Stelter L, Schnapauff D et al. CT-guided Interstitial Brachytherapy of Hepatocellular Carcinoma before Liver Transplantation: an Equivalent Alternative to Transarterial Chemoembolization? Eur Radiol 2015; 25: 2608-2616
96. Hickey RM, Lewandowski RJ, Salem R. Rationale of transcatheter intra-arterial therapies of hepatic cancers. Hepat Oncol 2014; 1: 285-291
97. Taylor I, Bennett R, Sherriff S. The blood supply of colorectal liver metastases. Br J Cancer 1978; 38: 749-756
98. Fajardo LF, Colby TV. Pathogenesis of veno-occlusive liver disease after radiation. Arch Pathol Lab Med 1980; 104: 584-588
99. Reed GB, Jr., Cox AJ, Jr. The human liver after radiation injury. A form of veno-occlusive disease. Am J Pathol 1966; 48: 597-611
100. Jones RJ, Lee KS, Beschorner WE et al. Venoocclusive disease of the liver following bone marrow transplantation. Transplantation 1987; 44: 778-783

101. Shulman HM, Hinterberger W. Hepatic veno-occlusive disease--liver toxicity syndrome after bone marrow transplantation. Bone Marrow Transplant 1992; 10: 197-214
102. DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). Semin Liver Dis 2002; 22: 27-42
103. Sangro B, Gil-Alzugaray B, Rodriguez J et al. Liver disease induced by radioembolization of liver tumors: description and possible risk factors. Cancer 2008; 112: 1538-1546
104. Lewandowski RJ, Sato KT, Atassi B et al. Radioembolization with 90Y microspheres: angiographic and technical considerations. Cardiovasc Intervent Radiol 2007; 30: 571-592
105. Maleux G, Heye S, Vaninbroukx J et al. Angiographic considerations in patients undergoing liver-directed radioembolization with 90Y microspheres. Acta Gastroenterol Belg 2010; 73: 489-496
106. Floridi C, Pesapane F, Angileri SA et al. Yttrium-90 radioembolization treatment for unresectable hepatocellular carcinoma: a single-centre prognostic factors analysis. Med Oncol 2017; 34: 174
107. Jia Z, Paz-Fumagalli R, Frey G et al. Resin-based Yttrium-90 microspheres for unresectable and failed first-line chemotherapy intrahepatic cholangiocarcinoma: preliminary results. J Cancer Res Clin Oncol 2017; 143: 481-489
108. Kalva SP, Rana RS, Liu R et al. Yttrium-90 Radioembolization as Salvage Therapy for Liver Metastases From Colorectal Cancer. Am J Clin Oncol 2017; 40: 288-293
109. Gil-Alzugaray B, Chopitea A, Inarrairaegui M et al. Prognostic factors and prevention of radioembolization-induced liver disease. Hepatology 2013; 57: 1078-1087
110. Chung YC, Chang YF. Significance of inflammatory cytokines in the progression of colorectal cancer. Hepatogastroenterology 2003; 50: 1910-1913
111. Nikiteas NI, Tzanakis N, Gazouli M et al. Serum IL-6, TNFalpha and CRP levels in Greek colorectal cancer patients: prognostic implications. World J Gastroenterol 2005; 11: 1639-1643

112. Wickremesekera JK, Chen W, Cannan RJ et al. Serum proinflammatory cytokine response in patients with advanced liver tumors following selective internal radiation therapy (SIRT) with (90)Yttrium microspheres. Int J Radiat Oncol Biol Phys 2001; 49: 1015-1021
113. Kim DK, Oh SY, Kwon HC et al. Clinical significances of preoperative serum interleukin-6 and C-reactive protein level in operable gastric cancer. BMC Cancer 2009; 9: 155
114. Soubrane C, Rixe O, Meric JB et al. Pretreatment serum interleukin-6 concentration as a prognostic factor of overall survival in metastatic malignant melanoma patients treated with biochemotherapy: a retrospective study. Melanoma Res 2005; 15: 199-204
115. Jakobs TF, Saleem S, Atassi B et al. Fibrosis, portal hypertension, and hepatic volume changes induced by intra-arterial radiotherapy with 90yttrium microspheres. Dig Dis Sci 2008; 53: 2556-2563
116. Paprottka PM, Schmidt GP, Trumm CG et al. Changes in normal liver and spleen volume after radioembolization with (90)Y-resin microspheres in metastatic breast cancer patients: findings and clinical significance. Cardiovasc Intervent Radiol 2011; 34: 964-972
117. Bayraktar UD, Seren S, Bayraktar Y. Hepatic venous outflow obstruction: three similar syndromes. World J Gastroenterol 2007; 13: 1912-1927
118. Narula N, Aloia TA. Portal vein embolization in extended liver resection. Langenbecks Arch Surg 2017; 402: 727-735
119. de Baere T, Teriitehau C, Deschamps F et al. Predictive factors for hypertrophy of the future remnant liver after selective portal vein embolization. Ann Surg Oncol 2010; 17: 2081-2089
120. Kishi Y, Madoff DC, Abdalla EK et al. Is embolization of segment 4 portal veins before extended right hepatectomy justified? Surgery 2008; 144: 744-751
121. Nanashima A, Sumida Y, Shibasaki S et al. Parameters associated with changes in liver volume in patients undergoing portal vein embolization. J Surg Res 2006; 133: 95-101
122. Narita M, Oussoultzoglou E, Chenard MP et al. Sinusoidal obstruction syndrome compromises liver regeneration in patients undergoing two-stage hepatectomy with portal vein embolization. Surg Today 2011; 41: 7-17

123. Rubbia-Brandt L, Audard V, Sartoretti P et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004; 15: 460-466
124. Elias D, De Baere T, Roche A et al. During liver regeneration following right portal embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma. Br J Surg 1999; 86: 784-788
125. Hoekstra LT, van Lienden KP, Doets A et al. Tumor progression after preoperative portal vein embolization. Ann Surg 2012; 256: 812-817; discussion 817-818
126. Kokudo N, Tada K, Seki M et al. Proliferative activity of intrahepatic colorectal metastases after preoperative hemihepatic portal vein embolization. Hepatology 2001; 34: 267-272
127. Ricke J, Seidensticker M, Ludemann L et al. In vivo assessment of the tolerance dose of small liver volumes after single-fraction HDR irradiation. Int J Radiat Oncol Biol Phys 2005; 62: 776-784
128. Powerski MJ, Scheurig-Munkler C, Hamm B et al. Impaired hepatic Gd-EOB-DTPA enhancement after radioembolisation of liver malignancies. J Med Imaging Radiat Oncol 2014; 58: 472-480
129. Yoneda N, Matsui O, Ikeno H et al. Correlation between Gd-EOB-DTPA-enhanced MR imaging findings and OATP1B3 expression in chemotherapy-associated sinusoidal obstruction syndrome. Abdom Imaging 2015; 40: 3099-3103
130. Essell JH, Schroeder MT, Harman GS et al. Ursodiol prophylaxis against hepatic complications of allogeneic bone marrow transplantation. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998; 128: 975-981
131. Ruutu T, Eriksson B, Remes K et al. Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. Blood 2002; 100: 1977-1983
132. Attal M, Huguet F, Rubie H et al. Prevention of regimen-related toxicities after bone marrow transplantation by pentoxifylline: a prospective, randomized trial. Blood 1993; 82: 732-736

133. Bianco JA, Appelbaum FR, Nemunaitis J et al. Phase I-II trial of pentoxifylline for the prevention of transplant-related toxicities following bone marrow transplantation. Blood 1991; 78: 1205-1211
134. Attal M, Huguet F, Rubie H et al. Prevention of hepatic veno-occlusive disease after bone marrow transplantation by continuous infusion of low-dose heparin: a prospective, randomized trial. Blood 1992; 79: 2834-2840
135. Forrest DL, Thompson K, Dorcas VG et al. Low molecular weight heparin for the prevention of hepatic veno-occlusive disease (VOD) after hematopoietic stem cell transplantation: a prospective phase II study. Bone Marrow Transplant 2003; 31: 1143-1149
136. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-386
137. Schmoll HJ, Van Cutsem E, Stein A et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 2012; 23: 2479-2516
138. Andreou A, Brouquet A, Abdalla EK et al. Repeat hepatectomy for recurrent colorectal liver metastases is associated with a high survival rate. HPB (Oxford) 2011; 13: 774-782
139. Otto G, Duber C, Hoppe-Lotichius M et al. Radiofrequency ablation as first-line treatment in patients with early colorectal liver metastases amenable to surgery. Ann Surg 2010; 251: 796-803
140. Berber E, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. J Clin Oncol 2005; 23: 1358-1364
141. Gillams AR, Lees WR. Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. Eur Radiol 2009; 19: 1206-1213
142. Sofocleous CT, Petre EN, Gonen M et al. CT-guided radiofrequency ablation as a salvage treatment of colorectal cancer hepatic metastases developing after hepatectomy. J Vasc Interv Radiol 2011; 22: 755-761
143. Collettini F, Lutter A, Schnapauff D et al. Unresectable colorectal liver metastases: percutaneous ablation using CT-guided high-dose-rate brachytherapy (CT-HDBRT). Rofo 2014; 186: 606-612

144. Lund CM, Vistisen KK, Dehlendorff C et al. The effect of geriatric intervention in frail elderly patients receiving chemotherapy for colorectal cancer: a randomized trial (GERICO). BMC Cancer 2017; 17: 448
145. Sogaard M, Thomsen RW, Bossen KS et al. The impact of comorbidity on cancer survival: a review. Clin Epidemiol 2013; 5: 3-29
146. Ostenfeld EB, Norgaard M, Thomsen RW et al. Comorbidity and survival of Danish patients with colon and rectal cancer from 2000-2011: a population-based cohort study. Clin Epidemiol 2013; 5: 65-74
147. Bakogeorgos M, Mountzios G, Kotsantis G et al. Chemotherapy compliance, tolerance and efficacy in elderly and non-elderly patients with metastatic colorectal cancer: a single institution comparative study. J BUON 2013; 18: 629-634
148. Jehn CF, Boning L, Kroning H et al. Influence of comorbidity, age and performance status on treatment efficacy and safety of cetuximab plus irinotecan in irinotecan-refractory elderly patients with metastatic colorectal cancer. Eur J Cancer 2014; 50: 1269-1275
149. Steele SR, Park GE, Johnson EK et al. The impact of age on colorectal cancer incidence, treatment, and outcomes in an equal-access health care system. Dis Colon Rectum 2014; 57: 303-310
150. Hasegawa H, Taniguchi H, Mitani S et al. Efficacy of Second-Line Bevacizumab-Containing Chemotherapy for Patients with Metastatic Colorectal Cancer following First-Line Treatment with an Anti-Epidermal Growth Factor Receptor Antibody. Oncology 2017; 92: 205-212
151. Ozaslan E, Serkan Topaloglu U, Inanc M et al. Efficacy and safety of cetuximab plus FOLFOX in second-line and third-line therapy in metastatic colorectal cancer. J BUON 2017; 22: 863-868
152. Yang Q, Huang Y, Jiang Z et al. Rechallenge of oxaliplatin-containing regimens in the third- or later-line therapy for patients with heavily treated metastatic colorectal cancer. Onco Targets Ther 2018; 11: 2467-2473
153. Gray BN. Colorectal cancer: the natural history of disseminated disease - a review. Aust N Z J Surg 1980; 50: 643-646
154. Osumi H, Shinozaki E, Suenaga M et al. RAS mutation is a prognostic biomarker in colorectal cancer patients with metastasectomy. Int J Cancer 2016; 139: 803-811

155. Jonasch E, Gao J, Rathmell WK. Renal cell carcinoma. BMJ 2014; 349: g4797
156. Violette P, Abourbih S, Szymanski KM et al. Solitary solid renal mass: can we predict malignancy? BJU Int 2012; 110: E548-552
157. Finelli A, Ismaila N, Bro B et al. Management of Small Renal Masses: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017; 35: 668-680
158. Thompson RH, Hill JR, Babayev Y et al. Metastatic renal cell carcinoma risk according to tumor size. J Urol 2009; 182: 41-45
159. Berger J, Fardoun T, Brassart E et al. Detailed analysis of morbidity following nephrectomy for renal cell carcinoma in octogenarians. J Urol 2012; 188: 736-740
160. Caputo PA, Zargar H, Ramirez D et al. Cryoablation versus Partial Nephrectomy for Clinical T1b Renal Tumors: A Matched Group Comparative Analysis. Eur Urol 2017; 71: 111-117
161. Ponsky L, Lo SS, Zhang Y et al. Phase I dose-escalation study of stereotactic body radiotherapy (SBRT) for poor surgical candidates with localized renal cell carcinoma. Radiother Oncol 2015; 117: 183-187
162. Siva S, Pham D, Kron T et al. Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: a prospective clinical trial. BJU Int 2017; 120: 623-630
163. Yamamoto T, Kadoya N, Takeda K et al. Renal atrophy after stereotactic body radiotherapy for renal cell carcinoma. Radiat Oncol 2016; 11: 72
164. Chawla SN, Crispen PL, Hanlon AL et al. The natural history of observed enhancing renal masses: meta-analysis and review of the world literature. J Urol 2006; 175: 425-431
165. Franzese C, Franceschini D, Di Brina L et al. Role of Stereotactic Body Radiation Therapy for the Management of Oligometastatic Renal Cell Carcinoma. J Urol 2019; 201: 70-76
166. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. J Clin Gastroenterol 2013; 47 Suppl: S2-6
167. Bolondi L, Burroughs A, Dufour JF et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012; 32: 348-359

168. El-Khoueiry AB, Sangro B, Yau T et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017; 389: 2492-2502
169. Kudo M, Finn RS, Qin S et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018; 391: 1163-1173
170. Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390
171. Zhu AX, Finn RS, Edeline J et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018; 19: 940-952
172. Bruix J, Takayama T, Mazzaferro V et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2015; 16: 1344-1354
173. Meyer T, Fox R, Ma YT et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. Lancet Gastroenterol Hepatol 2017; 2: 565-575
174. Seidensticker M, Streit S, Nass N et al. Modified transarterial chemoembolization with locoregional administration of sorafenib for treating hepatocellular carcinoma: feasibility, efficacy, and safety in the VX-2 rabbit liver tumor model. Diagn Interv Radiol 2016; 22: 378-384
175. Giannini EG, Bucci L, Garuti F et al. Patients with advanced hepatocellular carcinoma need a personalized management: A lesson from clinical practice. Hepatology 2018; 67: 1784-1796
176. Graf D, Vallbohmer D, Knoefel WT et al. Multimodal treatment of hepatocellular carcinoma. Eur J Intern Med 2014; 25: 430-437
177. Jain S, Dhingra S. Pathology of esophageal cancer and Barrett's esophagus. Ann Cardiothorac Surg 2017; 6: 99-109
178. Blom RL, Lagarde SM, van Oudenaarde K et al. Survival after recurrent esophageal carcinoma has not improved over the past 18 years. Ann Surg Oncol 2013; 20: 2693-2698

179. Mariette C, Balon JM, Piessen G et al. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. Cancer 2003; 97: 1616-1623
180. Nakagawa S, Kanda T, Kosugi S et al. Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. J Am Coll Surg 2004; 198: 205-211
181. Lordick F, Mariette C, Haustermans K et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27: v50-v57
182. Van Daele E, Scuderi V, Pape E et al. Long-term survival after multimodality therapy including surgery for metastatic esophageal cancer. Acta Chir Belg 2018; 118: 227-232
183. Baba Y, Watanabe M, Kawanaka K et al. Radiofrequency ablation for pulmonary metastases from esophageal squamous cell carcinoma. Dis Esophagus 2014; 27: 36-41
184. Matsui Y, Hiraki T, Gobara H et al. Percutaneous radiofrequency ablation for pulmonary metastases from esophageal cancer: retrospective evaluation of 21 patients. J Vasc Interv Radiol 2014; 25: 1566-1572
185. Islami F, Ferlay J, Lortet-Tieulent J et al. International trends in anal cancer incidence rates. Int J Epidemiol 2017; 46: 924-938
186. Glynne-Jones R, Nilsson PJ, Aschele C et al. Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 Suppl 3: iii10-20
187. Eng C, Chang GJ, You YN et al. The role of systemic chemotherapy and multidisciplinary management in improving the overall survival of patients with metastatic squamous cell carcinoma of the anal canal. Oncotarget 2014; 5: 11133-11142
188. Evesque L, Benezery K, Follana P et al. Multimodal Therapy of Squamous Cell Carcinoma of the Anus With Distant Metastasis: A Single-Institution Experience. Dis Colon Rectum 2017; 60: 785-791

7. Eidesstattliche Erklärung

Ich erkläre, dass ich die der Medizinischen Fakultät zur Habilitation eingereichte Habilitationsschrift mit dem Titel

Über die Weiterentwicklung der interventionellen Onkologie:
von der Technik bis zur Patientenselektion.

in der Klinik für Radiologie und Nuklearmedizin

mit Unterstützung durch Prof. Dr. Maciej Pech ohne sonstige Hilfe niedergeschrieben und bei der Abfassung keine anderen als die dort aufgeführten Hilfsmittel benutzt habe. Bei der Abfassung der Habilitationsschrift sind Rechte Dritter nicht verletzt worden.

Ich habe die Habilitationsschrift bisher an keiner in- oder ausländischen Hochschule oder Universität zur Habilitation eingereicht.

Ich übertrage der Medizinischen Fakultät der Otto-von-Guericke-Universität das Recht, weitere Kopien meiner Habilitationsschrift herzustellen und zu vertreiben.

Magdeburg, den 07.08.2019

Dr. med. Robert Friedrich Damm

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9. Anhang

Abkürzungsverzeichnis:

ACA	*Anal Cancer*, Analkarzinom
BC	Bronchialcarcinom, Bronchialkarzinom
BCLC	*Barcelona Clinic Liver Cancer*
BSC	*Best supportive care*, bestmöglich unterstützende Pflege
CA	*Cryoablation*, Kryoablation
CCC	*Cholangiocellular carcinoma*, Cholangiozelluläres Karzinom
CLOCC	*Chemotherapy + Local ablation versus chemotherapy*
CMILD	*Combined modality induced liver disease*, durch kombinierte Modalitäten induzierte Lebererkrankung
CRC	*Colorectal cancer*, Kolorektales Karzinom
CT	Computertomographie
CTCAE	*Common Terminology Criteria in Adverse Events* Allgemeine Terminologiekriterien für unerwünschte Ereignisse
CTV	*Clinical target volume*, klinisches Zielvolumen
ECA	*Esophageal Cancer*, Ösophaguskarzinom
eGFR	*epidermal growth factor receptor*, epidermaler Wachstumsfaktorrezeptor
FLR	*Future liver remnant*, zukünftige Restleber
FOXFIRE	*5-Fluorouracil, Oxaliplatin and Folinic Acid ± Interventional Radio-Embolisation*
Gd-EOB-DTPA	Gadoxetsäure
HCC	*Hepatocellular carcinoma*, Hepatozelluläres Karzinom
iBT	Interstitielle Brachytherapie
IRE	Irreversible Elektroporation
KDOQI	*Kidney Disease Outcomes Quality Initiative*
LTC	*Local tumor control*, lokale Tumorkontrolle
mCRC	*Metastatic colorectal Cancer*, metastasiertes kolorektales Karzinom
MRT	Magnetresonanztomographie
MWA	*Microwave ablation*, Mikrowellenablation
NCC	Nierencellcarcinom, Nierenzellkarzinom

OS	*Overall survival*, Gesamtüberleben
PFS	*Progression-free survival*, Progressionsfreies Überleben
PVE	*Portal vein embolization*, Pfortaderembolisation
RFA	*Radiofrequency ablation*, Radiofrequenzablation
RILD	*Radiation induced liver disease*, Strahleninduzierte Lebererkrankung
RE	Radioembolisation
REILD	*Radioembolization induced liver disease*, Radioembolisationsinduzierte Lebererkrankung
RNA	*ribonucleic acid*, Ribonukleinsäure
SARAH	*Sorafenib versus Radioembolization in Advanced Hepatocellular Carcinoma*
SBRT	*Stereotactic body radiotherapy*, stereotaktische Bestrahlung
SIRFLOX	*Selective Internal Radiation Therapy and 5-Fluorouracil + Oxaliplatin*
SIRCCA	*SIRT followed by CIS-GEM Chemotherapy Versus CIS-GEM Chemotherapy Alone*
SIRT	Selektive Interne Radiotherapie
SIRveNIB	*Study to compare Selective Internal Radiation Therapy versus Sorafenib in locally advance hepatocellular carcinoma*
SOS	*sinusoidal obstruction syndrome*, Sinusoidales Obstruktionssyndrom
TACE	Transarterielle Chemoembolisation
VEGF	*vascular endothelial growth factor,* vaskulär-endothelialer Wachstumsfaktor
VOD	*Veno-occlusive disease*, Venenverschlusserkrankung
Y90-RE	Yttrium90-Radioembolisation

Tabelle 1: Verfahren der interventionellen Onkologie mit Wirkprinzipien und Einsatzgebiet.

Technik	**Abkürzung**	**Wirkprinzip**	**Verbreitete Einsatzgebiete/ behandelnde Veröffentlichung**
Lokal-ablative Verfahren			
Radiofrequenzablation	RFA	Thermische Koagulationsnekrose	Lunge, Leber, Nieren **Veröffentlichung 9, 17**
Mikrowellenablation	MWA		Lunge, Leber, Nieren
Kryoablation	CA	Lokale Vereisung	Leber, Nieren
Interstitielle Brachytherapie	iBT	Hochdosis-bestrahlung	Lunge, Leber, Nieren, Nebennieren, Lymphknoten **Veröffentlichung 2, 5, 6, 10, 11, 12, 13, 14, 15, 16,17, 18, 19, 20**
Irreversible Elektroporation	IRE	Elektrische Zellmembran-schädigung	Lunge, Leber, Nieren, Pankreas
Lokoregionäre Verfahren			
Transarterielle Chemoembolisation	TACE	Regionale Embolisation und Chemotherapie	Leber, Nieren **Veröffentlichung 15**
Transarterielle Radioembolisation (Selektive Interne Radiotherapie)	TARE (SIRT)	Regionale Embolisation und Radiotherapie	Leber **Veröffentlichung 1, 2, 3, 4, 7, 8, 11**

Tabelle 2: Lokale Tumorkontrolle (LTC) der interstitiellen Brachytherapie (iBT) sowie Überleben (OS) nach Organen, Entitäten und Dosisverschreibung.

Organ	**Entität**	**Zieldosis**	**LTC (Patienten/ Läsionen)**	**Medianes OS (Patienten)**	**behandelnde Veröffentlichung**
Leber	HCC	15 Gy	-	~29 Monate (n=37)	**Veröffentlichung 15**
	NCC	15 Gy	92,6% (n=14/n=54)	51,2 Monate (n=14)	**Veröffentlichung 18**
	mCRC	20 Gy	-	18,1 Monate (n=176)	**Veröffentlichung 11**
Lunge			-	29,6 Monate (n=29)	
Lymphknoten/ Retroperitoneum			-	17,0 – 26,7 Monate (n=17)	
Niere	NCC	15 Gy, Rezidive 20 Gy	85,0% (n=16/n=20) 95,0% (n=2/n=2)	27,0 Monate (n=16)	**Veröffentlichung 20**
gemischt	mECA	15 Gy	85,7% (n=11/n=21)	13,8 Monate (n=11)	**Veröffentlichung 14**
	mACA		97,4% (n=7/n=38)	25,2 Monate (n=7)	**Veröffentlichung 10**

Tabelle 3: Strahlentherapeutische Komplikationen nach interstitieller Brachytherapie (iBT).

Therapie-organ	**Risiko-organ**	**Patienten-anzahl**	**Komplikation (Häufigkeit)**	**Risikofaktor(en)**	**behandelnde Veröffentlichung**
Leber	Leber	n=22	Funktionelle Leber-parenchymschädigung mit vs. ohne Präventivmedikation (45,5% vs. 90,9%)	Schwellendosis mit vs. ohne Medikation 19,1 Gy vs. 14,6 Gy	**Veröffentlichung 5**
		n=192	Hepatische Dekompensation (n=1/0,5%)	Steatohepatitis	**Veröffentlichung 6**
	Intestinum	n=192	Ulkus (n=3/4,3%)	Punktdosis >14,0 Gy	
	Gallenwege	n=102	Cholestase (n=22/22%)	Punktdosis >20,8 Gy	**Veröffentlichung 13**
Niere	Niere	n=16	Hämodialyse (n=1/6,3%)	Prätherapeutische Niereninsuffizienz KDOQI °IV	**Veröffentlichung 20**

Tabelle 4: Interventionelle Komplikationen nach interstitieller Brachytherapie (iBT).

Therapie-organ	**Risiko-organ**	**Patienten-anzahl**	**Komplikation (Häufigkeit)**	**Risikofaktor(en)**	**behandelnde Veröffentlichung**
Leber	Leber	n=192	Hämorrhagie (n=5/2,6%) Leberabszess (n=4/2,1%) Akute Cholestase (n=1/0,5%)	HCC/Leberzirrhose - -	**Veröffentlichung 6**
		n=100	Stichkanal-metastasierung (n=7/7,0%)	-	**Veröffentlichung 16**
	Rumpfwand	n=100	Stichkanal-metastasierung (n=2/2%)		
Niere	Niere	n=16	Hämorrhagie (n=1/6,3%)	-	**Veröffentlichung 20**

Tabelle 5: Beobachtungen zur Leberfunktion und dem Therapieansprechen bei verschiedenen, wissenschaftlichen Betrachtungen der Y90-Radioembolisation.

Methodik	**Gruppen/ Stratifizierung**	**Effektivitätsvariable(n)**	**behandelnde Veröffentlichung**
Therapeutischer Ansatz bzw. Rationale			
Anatomische Separation in zwei lobäre Sitzungen	Bilobäre Y90-RE (mCRC-Subgruppe)	OS: 9,7 Monate* (9,8 Monate)	**Veröffentlichung 1**
	Sequenzielle Y90-RE (mCRC-Subgruppe)	OS: 17,5 Monate* (15,6 Monate)	
Wiederholte Radioembolisation bei mindestens einem Leberlappen	-	OS: 18 Monate CTCAE °III: 13% Ø REILD	**Veröffentlichung 4**
Evaluierung des prätherapeutischen Zytokinprofils	IL6 ≤ 6,53 pg/ml; IL8 ≤ 60,8 pg/ml	OS: 13,2 Monate*; 13,2 Monate*	**Veröffentlichung 8**
	IL6 > 6,53 pg/ml IL8 > 60,8 pg/ml	OS: 5,0 Monate*; 5,1 Monate*	
Hypertrophieinduktion			
Sequenzielle Radioembolisation, (Volumetrie 4-6 Wochen nach erster Y90-RE und vor zweiter Y90-RE)	Erstbehandelter Leberlappen	Volumen im Zeitverlauf: - 9%* / - 18%* / - 9%	**Veröffentlichung 1**
	Zeitlich versetzter Leberlappen	Volumen im Zeitverlauf: + 13%* / + 11% / + 25%*	
Hypertrophie des Restlebervolumens nach Radioembolisation versus Pfortaderembolisation	Y90-RE (Radioembolisation)	FLR-Hypertrophie: 29,0%*	**Veröffentlichung 3**
	PVE (Pfortaderembolisation)	FLR-Hypertrophie: 61,5%*	
Medikamentöse Therapie			
Protektive Medikation zur Vermeidung der REILD (Modell: Radiogene Dysfunktion nach interstitieller Brachytherapie im hepatozytenspezifischen MRT)	Medikationsgruppe (Ursodeoxycholsäure, Pentoxifyllin, Enoxaparin)	Isodose der hepatozytären Dysfunktion:19,06 Gy*	**Veröffentlichung 5**
	Kontrolle	Isodose der hepatozytären Dysfunktion: 14,64 Gy*	
* Erreichen einer statistischen Signifikanz (p<0,05)			

Tabelle 6: Dargestellte Verfahren der interventionellen Onkologie nach Tumorentität.

Entität	**Therapie-verfahren**	**Patienten-anzahl**	**LTC/ Medianes PFS**	**Medianes OS (Stratifizierungen*)**	**behandelnde Veröffentlichung**
gemischt	RFA	n=79	85,3%	27,0 Monate (Lunge)	**Veröffentlichung 9**
mCRC		n=60	-	24,4 Monate (Lunge) 26,7 Monate (Leber)	**Veröffentlichung 11**
	iBT	n=192	-	29,6 Monate (Lunge) 18,1 Monate (Leber)	
	Y90-RE	n=96	-	6,7 Monate	**Veröffentlichung 7, 11**
		n=22	-	9,8 Monate (bilobär) 15,6 Monate (sequenziell)	**Veröffentlichung 1**
HCC	iBT	n=37	- / ~15 Monate	~29 Monate	**Veröffentlichung 15**
	TACE	n=40	- / ~7 Monate	~24 Monate	
NCC	iBT	n=16	85,0% - 95,0% / -	27,0 Monate	**Veröffentlichung 20**
mNCC		n=14	92,6% / 3,4 Monate	51,2 Monate	**Veröffentlichung 18**
mECA		n=11	85,7% / 3.4 Monate	13,8 Monate	**Veröffentlichung 14**
mACA		n=7	97,4% / 3,3 Monate	25,2 Monate	**Veröffentlichung 10**

* Stratifizierungen:

Metastasenorgan - Lunge oder Leber

Y90-RE - bilobäre Therapie (Ganzleberbehandlung) oder sequenzielle Therapie (zweizeitig-lobäre Behandlung)

10. Originale der Publikationen

Veröffentlichung 1

Hepatic toxicity after radioembolization of the liver using (90)Y-microspheres: sequential lobar versus whole liver approach.

Seidensticker R, Seidensticker M, **Damm R**, Mohnike K, Schütte K, Malfertheiner P, Van Buskirk M, Pech M, Amthauer H, Ricke J.

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Hepatic Toxicity After Radioembolization of the Liver Using ^{90}Y-Microspheres: Sequential Lobar Versus Whole Liver Approach

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Abstract
Purpose ^{90}Y-radioembolization (RE) is a promising technique for delivering high doses of radiation to liver tumors but may result in compromise of liver function. To gain further perspective, we evaluated the toxicity rates of sequential lobar versus "whole liver" ^{90}Y-radioembolization.
Methods Thirty-four patients with liver malignancy in noncirrhotic livers were included; ^{90}Y-radioembolization was performed as either whole liver or sequential lobar treatment in 17 patients each. Standard clinical and liver specific laboratory parameters as well as MR imaging before treatment and at follow-up (6 and 12 weeks) after radioembolization were evaluated for toxicity using the Common Terminology Criteria for Adverse Events (CTCAE). Volumetry of the liver, tumor, and spleen and measurement of portal vein diameter also were performed.
Results Three months after whole liver RE, 14 liver-related grade 3/4 events were recorded versus 2 events after sequential lobar treatment ($P < 0.05$). Three patients treated with whole liver RE suffered from radioembolization-induced liver disease (REILD). Pathological increases in bilirubin at 3 months were observed for the whole liver group only (52.3 vs. 18.7 μmol/l, $P = 0.012$). Total liver volume did not change significantly in either group, but shrinkage of the initially treated hepatic lobe with compensatory hypertrophy of the subsequently treated lobe was observed in the sequential lobar group ($P < 0.05$). Portal vein diameter increased significantly in whole liver-treated patients only (+17% vs. +6.6%, $P = 0.043$).
Conclusions Noncirrhotic patients undergoing sequential lobar radioembolization had less hepatic toxicity compared to whole liver embolization. The sequential approach should be the preferred strategy.

Keywords Yttrium-90 · Hepatic toxicity · Radiation induced liver disease · RILD · REILD · Hepatic metastases · Local ablation

Introduction

^{90}Y-radioembolization (RE) delivers radionuclide embedded resin microspheres to liver tumors via the hepatic artery. Upon arterial injection, the microspheres selectively embolize in the tumor vasculature as in comparison to normal hepatic parenchyma [1]. RE has shown promising tumor control rates in patients with both primary and secondary liver malignancies [2, 3]. Although prospective randomized data are still scarce, diligent analyses of large, phase II single arm cohorts have suggested prognostic benefit, specifically in hepatocellular carcinoma (HCC) and colorectal cancer (CRC) [2, 4–9]. A recent comparative analyses of 250 patients suffering from advanced HCC demonstrated not only favorable results in BCLC B and C patients but also better tolerance to radioembolization

Ricarda Seidensticker, Max Seidensticker contributed equally to this work.

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compared with TACE in diffuse disease or patients presenting with portal vein thrombosis [10].

However, ^{90}Y-radioembolization is technically demanding and associated with a considerable risk of complications if not performed appropriately. Whereas radiation pneumonitis has virtually disappeared with the introduction of pretreatment Technetium-99m-macroaggreated albumin (^{99m}Tc-MAA) injection in the hepatic artery and concomitant scintigraphy [11], mechanisms of radiation induced liver disease due to RE are still not fully understood. Sangro et al. published a landmark paper in 2008 that differentiated between external radiation and radioembolization-induced liver disease (REILD) in patients without chronic liver disease. They also reported risk factors for the development of symptomatic liver function impairment after RE. Whereas radiation induced liver disease from external radiation is characterized by symptomatic ascites and elevated liver enzymes but not bilirubin, radioembolization-induced liver disease presents with ascites, nonelevated transaminases (except for ALP and GGPT), and significant bilirubin increase. Patients at risk for REILD were younger, had a lower body mass index (BMI), and had undergone more previous chemotherapies. Age, bilirubin at baseline, treatment approach (whole-liver vs. unilobar), and the amount of activity administered relative to the total volume treated were all found to be independent risk factors for the development of REILD [12].

To date, no protective agents for the prevention of radiation or radioembolization-induced liver disease have been described, although few drugs are considered to prevent the histopathologically related veno-occlusive disease (VOD) that occurs after bone-marrow transplantation [13–15]. Thus, dose reduction has to be considered in high-risk patients. However, reduced radiation activity may negatively affect response rates. The objective of the current retrospective analysis was to determine whether a sequential approach, i.e., delivering partitioned doses to the left and right liver lobe at an interval of 4–6 weeks, was effective in mitigating symptomatic radioembolization induced liver disease. Two patient cohorts were examined: one receiving whole liver radioembolization with resin microspheres at a single time point; and the other undergoing sequential treatments to allow for functional recovery of the previously affected lobe. The time interval applied was derived from previous experiences describing significant liver recovery 6 weeks after single fraction treatment of focal liver volumes [16, 17].

Patients and Methods

Study Design

Radioembolization has been performed at our institution since 2004. To avoid influence of learning curve and patient selection, only patients treated with ^{90}Y-radioembolization between 2006 and 2009 were selected. Whereas in 2006 and 2007 ^{90}Y-radioembolization was performed as a whole-liver treatment in a single session, sequential bilobar treatments with an intervening interval of 6 weeks were performed thereafter. The goal of this retrospective analysis was to compare hepatic toxicity within 3 months after ^{90}Y-RE for whole liver versus sequential lobar treatments.

Liver function was evaluated by laboratory parameters, including liver function tests and MR imaging, to assess surrogates of portal hypertension and liver impairment was performed. Additional clinical parameters, including ascites, pleural effusion, and changes in liver and splenic volume, and portal vein diameter also were assessed.

Patient Selection and Eligibility Criteria

All records of patients undergoing ^{90}Y-radioembolization during 2006–2009 ($n = 139$) were reviewed. Patients were excluded from the analysis for the following reasons: patients presenting with HCC and/or cirrhosis ($n = 37$); patients undergoing any ablative therapy of the liver within 3 months before or after RE ($n = 21$); patients receiving any cytotoxic therapy within 3 months after RE ($n = 0$); patients with incomplete data acquisition during follow-up ($n = 19$); death within 3 months after RE not related to RE ($n = 11$); incomplete sequential radioembolization (i.e., only single lobe treatment) ($n = 12$); or prolonged interval between sequential RE (>8 weeks) ($n = 5$).

Thirty-four patients (14 female, 20 male; mean age, 63 years) were included in the analysis. Seventeen patients each were allocated to the whole-liver or sequential-lobar treatment group. Tumor types in the bilobar group included colorectal cancer ($n = 15$), pancreatic cancer ($n = 1$), and urothelial cell carcinoma ($n = 1$). Tumor types in the sequential treated group included colorectal cancer ($n = 7$), breast cancer ($n = 6$), and urothelial cell carcinoma, lung cancer, cholangiocellular carcinoma (CCC), and gastrointestinal stromal tumor (GIST) ($n = 1$ each). All patients were deemed inoperable; the patients either had no further chemotherapeutic options or refused further chemotherapy. Decision to treat with RE was made by a tumor board that included medical and surgical oncologists.

Prior Treatments

The type and number of chemotherapy lines before RE were documented due to their potential radio sensitizing or liver toxic properties [18–21]. Line of chemotherapy was defined as follows: patients who progressed during adjuvant chemotherapy were deemed to have failed a line of chemotherapy. Additionally patients who had an interruption in the delivery of a chemotherapy regimen, who had

one of the components of a combination terminated or who had one fluoropyrimidine substituted for another were regarded as having received one line of chemotherapy. All prior liver surgery and ablative interventions, including location and frequency also were documented.

Technique of ^{90}Y-Radioembolization

RE was performed employing Yttrium-90 (^{90}Y) resin microspheres (SIR-Spheres®, Sirtex Medical, Lane Cove, Australia). ^{90}Y is characterized by a mean energy of 0.96 MeV and a half-life of 64 h. It is coupled to resin microspheres (20–60 μm) and infused selectively via the hepatic arteries using a transfemoral approach. A detailed account of our treatment protocol has been published previously [22, 23].

Before RE, a meticulous celiac and superior mesenteric angiography was undertaken to map the hepatic arterial tree, identify arterial feeders to the gastrointestinal tract, and coil embolize the gastroduodenal and right gastric arteries and any other gastrointestinal tract feeders. Once the hepatic arterial blood supply had been isolated, the ^{99m}Tc-MAA injection (150 MBq, ^{99m}Tc-LyoMAA, Covidien, Neustadt/Donau, Germany) was delivered into the hepatic artery and a gamma camera (E.CAM 180, Siemens, Erlangen, Germany) determined the extent of hepatopulmonary shunting. A SPECT scan of the upper abdomen was performed and if nontarget extrahepatic seeding of ^{99m}Tc-MAA was found, the intra-arterial angiography procedure was repeated and modified accordingly.

The activity of ^{90}Y resin microspheres was calculated by the body surface area (BSA) method. With this method, the activity depends on the body surface area as well as on the liver tumor involvement. It was reduced if there was excessive liver-lung shunting (>10%). Up to 2 weeks later, ^{90}Y resin microspheres were delivered via a temporary transfemoral catheter placed in the proper hepatic artery as a single whole-liver administration or selectively in the right and left lobar arteries as a sequential treatment of each lobe 4–8 weeks apart. All patients received the whole calculated dose, thus treatment was deemed technically successful in all patients. All patients were admitted the day before the procedure and typically discharged 2 days later.

Image Assessments and Volumetry

Routine baseline and follow-up imaging consisted of MRI using the hepatocyte selective contrast agent gadoxetic acid (Gd-EOB-DTPA, Primovist®, Bayer Schering Pharma Diagnostic Imaging, Leverkusen, Germany) before, 6 weeks, and every 3 months after RE. We employed a 1.5 Tesla system (Achieva 1.5T®, Philips, Best, The Netherlands).

For tumor and liver volumetry (whole liver, left/right lobe [excluding the tumor, inferior vena cava, gall bladder, and benign liver tumors, such as cysts]), T1-weighted gradient echo (GRE) sequences 20 min after i.v. administration of 0.025 mmol/KG/BW Gd-EOB-DTPA were used. Axial T2-weighted spin echo (SE) sequences served for determination of splenic volumes as well as ascites and pleural effusion. Dynamic axial T1-weighted GRE sequences in portalvenous phase were used to measure the diameter of the portal vein. Volumetry and metric measurements were performed with the image processing software Osirix (©Antoine Rosset, 2003-2011).

Clinical and Toxicity Assessments at Baseline and During Follow-Up

All patients had undergone standard clinical (physical examination and anamnesis) and laboratory examinations, including liver-related parameters at first presentation, before RE and during follow-up visits at 6 weeks and every 3 months after RE. Laboratory tests included the following liver related parameters: total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGPT), and albumin.

Definitions

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.02 (National Cancer Institute, USA) was used for toxicity assessments of laboratory values as well as ascites and pleural effusion. REILD was diagnosed by clinical presentation of jaundice and ascites and a bilirubin increase of >50 μmol/l according to the definition by Sangro et al. [12].

Statistical Analyses

Statistical analyses employed SAS® version 9.2 software (SAS Institute Inc., Cary, NC, USA) and used Student's *t* test and analysis of covariance for metric variables. Comparisons of nonmetric variables were conducted using the Wilcoxon and Mann–Whitney tests. Further comparative analyses included Fisher's exact test. Survival data were assessed using the Kaplan–Meier analysis with the log-rank test for comparison of groups. A P value <0.05 was considered significant.

The study was conducted and the manuscript was written following the reporting standards for radioembolization of hepatic malignancies [24].

Results

Patient characteristics

Baseline patient characteristics for both cohorts are outlined in Table 1. There were no significant differences between the groups regarding age, gender, ^{90}Y-dosage, extrahepatic metastases, prior chemotherapies, and prior liver interventions.

Patients with sequential lobar RE underwent the second treatment procedure after an interval of 38.9 ± 10.3 days. Follow-up visits were scheduled 6.1 ± 0.8 weeks as well as 12.9 ± 2.0 weeks after the final RE with no statistical difference between the two groups.

Liver Toxicity Assessments

A significant increase in median ascites grade (including grade 0–4) was found for both groups 6 and 12 weeks after the completion of RE (sequential RE $P = 0.011$ and 0.005, respectively and whole-liver RE $P = 0.011$ and 0.018, respectively). Increases in pleural effusion (median, including grade 0–4) were only present 3 months after whole liver RE ($P = 0.043$). Pleural effusion showed a significant correlation with prior pulmonary interventions (6 weeks after RE $r = 0.397$; $P = 0.011$). However, grade 3 or 4 pleural effusions in patients with prior local ablation of pulmonary metastases were excluded from the liver toxicity analysis.

Manifestation of symptomatic REILD was found in three patients who were previously treated with whole liver RE but not in the sequential lobar group. Two of these patients were diagnosed clinically; one was confirmed by fine-needle biopsy demonstrating sinusoidal obstruction secondary to veno-occlusive disease (Fig. 1). In all of these patients, progression of hepatic metastases as origin of liver decompensation could be excluded.

For evaluation of overall liver toxicity, CTCAE 4.02 were used to record grade 3 or 4 events: hyperbilirubinemia, pleural effusion (excluding events in patients with prior local ablative interventions to the lungs), ascites, and clinical findings associated with RE. A summary is displayed in Table 2. A higher number of grade 3 or 4 events were found after whole-liver treatment at 3 months post-therapy (14 events) in contrast to two events after sequential lobar treatment ($P = 0.01$).

Apart from a significant difference of the albumin level (whole-liver group in mean 38.6 g/l versus 42.6 g/l in the sequential group, $P = 0.04$, both within normal ranges), baseline laboratory parameters were not significantly

Table 1 Patient characteristics

	Whole liver RE ($n = 17$)	Sequential lobar RE ($n = 17$)	P value
Age (year)			
Mean	64.7	61.3 years	n.s.
SD	±7.5	±9.5 years	
Gender			
Male	13	7	n.s.
Female	4	10	n.s.
Dosage			
Mean	1.67 GBq	1.85 GBq	n.s.
SD	± 0.35 GBq	± 0.26 GBq	
Cancer history			
Primary tumor			
Overall	CRC ($n = 22$), breast cancer ($n = 6$), urothelial cancer ($n = 2$), CCC, GIST, lung cancer, pancreatic cancer ($n = 1$)		
Extrahepatic metastases			
Pulmonary	9	5	n.s.
Osseous	1	3	n.s.
Other	3	4	n.s.
Prior liver treatments			
Resection	7	3	n.s.
Local ablation[a]	5	3	n.s.
Prior CTX			
No. of patients	14	16	n.s.
Mean cycles	3.6	2.9	
SD	±1.2	±2.2	n.s.

n.s. not statistically significant

[a] e.g., radiofrequency ablation, thermoablation

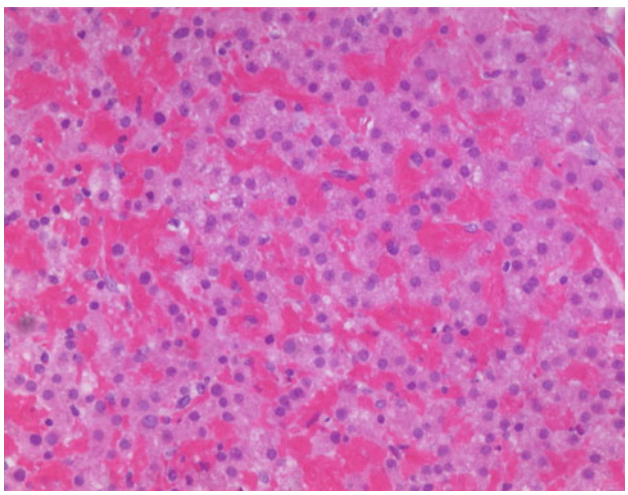

Fig. 1 Liver biopsy of a patient treated with whole-liver ^{90}Y-radioembolization 6 weeks previously. Histology shows severe sinusoidal congestion with atrophy of hepatocytes. Hematoxylin-eosin, original magnification: ×200

Table 2 Adverse events after treatment with whole liver and sequential lobar ^{90}Y-radioembolization

	Whole liver RE ($n = 17$)	Sequential lobar RE ($n = 17$)	P value
Patients with REILD[a]	3	0	n.a.
No. of CTCAE grade 3/4 events			
Bilirubin			
6 weeks	2	0	n.a.
3 months	6	1	n.a.
Ascites			
6 weeks	1	0	n.a.
3 months	3	0	n.a.
Pleural effusion			
6 weeks	0	0	n.a.
3 months	3	1	n.a.
Other			
6 weeks	0	0	n.a.
3 months	2[b]	0	n.a.
Overall			
6 weeks	3	0	n.s.
3 months	14	2	0.01

n.s. not statistically significant

[a] Severe ascites, jaundice, and bilirubin >50 mmol/l [12]

[b] III portal hypertension, $n = 1$; III PVT, $n = 1$

different. Laboratory parameters revealed a significant elevation of total bilirubin 3 months after whole liver RE compared with baseline (13.9–52.3 µmol/l, $P < 0.05$) exceeding normal ranges (Fig. 2) but not sequential lobar RE ($P > 0.05$). The two groups also were compared using relative changes in bilirubin from baseline to 3 months (Table 3). There was a significantly higher bilirubin elevation 3 months after whole-liver RE vs. sequential RE ($P = 0.012$), which reflected abnormal values (52.3 µmol/l).

As shown in Table 3, AST and ALP showed a significant increase from baseline to 3 months after sequential lobar RE (0.89–1.29 µmol/s.l and 3.07–5.31 µmol/s.l, respectively, $P < 0.05$), whereas total absolute values of these parameters were comparable to whole liver RE after 3 months. ALT levels showed a significant elevation 3 months after sequential RE versus whole-liver RE (0.49 µmol/s.l vs. 0.92 µmol/s.l, $P = 0.016$). Albumin was significantly reduced 6 weeks after sequential RE and 3 months after whole-liver RE ($P < 0.05$), respectively.

Liver Volume

The results of MRI based liver and tumor volume are presented in Table 4. The mean volume of liver or tumor did not differ significantly between the groups before RE. At baseline, 6 weeks, and 3 months after RE, there were no significant changes in whole liver volumes for whole-liver or sequential RE.

Table 5 presents changes in individual lobar volumes for patients who received sequential lobar treatments. The mean liver lobe volume after the first lobar treatment decreased significantly by 91 ml compared with baseline within 6 weeks until the second lobar treatment (−9%,

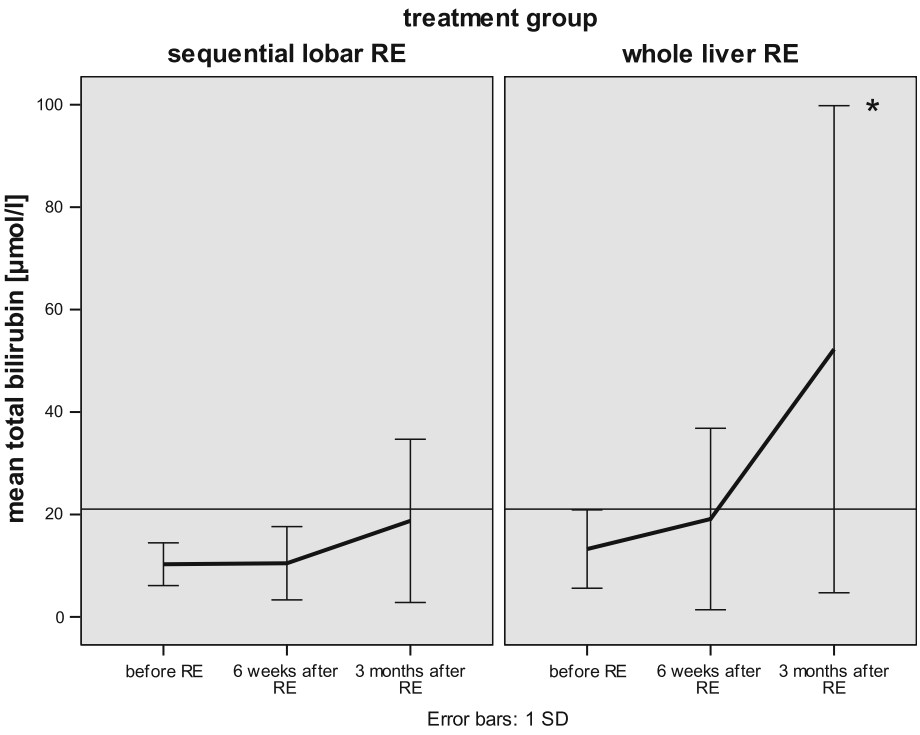

Fig. 2 Bilirubin levels after sequential-lobar and whole-liver ^{90}Y-radioembolization. Course of mean total bilirubin levels after sequential-lobar and whole-liver RE. The *upper normal limit* is indicated with a *continuous line* at 21 µmol/l. Significant elevation of the total bilirubin after whole liver RE (*) with a mean total bilirubin above the upper normal limit 3 months after RE. No significant elevation after sequential lobar RE with a mean total bilirubin within the normal limit after completed RE

Table 3 Liver function after whole liver and sequential lobar treatment with ^{90}Y-radioembolization

	Whole liver RE ($n = 17$)	Sequential lobar RE ($n = 17$)	P value[c]
Bilirubin (μmol/L)			
Baseline	13.9 ± 7.66	10.22 ± 4.18	
6 weeks	19.06 ± 17.75	10.41 ± 7.17	n.s.
3 months	52.27 ± 47.63[b]	18.7 ± 15.96	0.012
ALT (μmol/s.l)			
Baseline	0.58 ± 0.32	0.66 ± 0.57	
6 weeks	0.53 ± 0.27	0.72 ± 0.47	n.s.
3 months	0.49 ± 0.18	0.92 ± 0.67	0.016
AST (μmol/s.l)			
Baseline	1.03 ± 0.63	0.89 ± 0.54	
6 weeks	1 ± 0.72	0.89 ± 0.28	n.s.
3 months	1.28 ± 0.92	1.29 ± 0.44[b]	n.s.
ALP (μmol/s.l)			
Baseline	4.39 ± 3.41	3.07 ± 2.43	
6 weeks	4.49 ± 3.98	2.87 ± 1.24	n.s.
3 months	5.28 ± 5.15	5.31 ± 2.83[b]	n.s.
GGPT (μmol/s.l)			
Baseline	6.19 ± 6.17	4.69 ± 6.79	
6 weeks	5.36 ± 6.36	2.46 ± 1.76	n.s.
3 months	4.23 ± 2.89	6.48 ± 5.21	n.s.
Albumin (g/L)			
Baseline[a]	38.59 ± 4.03	42.56 ± 3.06	
6 weeks	35.51 ± 10.71	39.81 ± 3.52[b]	n.s.
3 months	34.29 ± 7.72[b]	39.55 ± 6.14	n.s.

n.s. not statistically significant

Data are means ± standard deviations unless otherwise indicated

[a] Significant difference at baseline ($P < 0.05$)

[b] Significant difference from baseline ($P < 0.05$)

[c] Group comparison using changes from baseline

Table 4 MRI volumetry after treatment with whole liver and sequential lobar ^{90}Y-radioembolization

	Whole liver RE ($n = 17$)	Sequential lobar RE ($n = 17$)	P value[c]
Liver volume (ml)			
Baseline	2073 ± 829	1641 ± 460	
6 weeks	1919 ± 712	1536 ± 444	n.s.
	−4.3%	−2.7%	
3 months	2083 ± 864	1708 ± 760	
	+2.9%	+2.7%	
Tumor volume (ml)			
Baseline	490 ± 541	219 ± 206	
Tumor load (%)			
Baseline	20 ± 14.4%	12.4 ± 10.4%	
Spleen volume (ml)			
Baseline[a]	420 ± 247	205 ± 136	
6 weeks	523 ± 301[b]	263 ± 156[b]	n.s.
	+28%	+39%	
3 months	543 ± 351[b]	310 ± 189[b]	n.s.
	+30%	+64%	
Portal vein diameter (mm)			
Baseline	12.3 ± 2.1	11.6 ± 1.4	
6 weeks	14 ± 2.1[b]	12.4 ± 1.5	0.031
	+16%	+8%	
3 months	14.2 ± 2.1[b]	12.3 ± 2	0.043
	+17%	+6%	

n.s. not statistically significant

Data are means ± standard deviations unless otherwise indicated

[a] Significant difference at baseline ($P < 0.05$)

[b] Significant difference from baseline ($P < 0.05$)

[c] Group comparison using relative changes in volume/diameter

$P = 0.016$). Further volume reduction was observed at 6 weeks after completed RE (−180 ml, −18%, $P = 0.002$) with a following increase at 3 months after completed RE (−93 ml, −9%, not significant). In contrast, the second treated liver lobe showed a significant mean volume increase 6 weeks after contralateral treatment of the first treated lobe (+86 ml, +13%, $P = 0.011$) and 3 months after completed RE (of the second treated lobe) (+160 ml, +25%, $P = 0.046$).

Spleen Volume

As illustrated in Table 4, splenic volumes increased significantly from baseline to 6 weeks and 3 months after completion of RE in both whole-liver (6 weeks: +28%, 3 months: +38%, $P < 0.05$) and sequential lobar (6 weeks: +39%, 3 months: +64%, $P < 0.05$) groups. The relative increase in splenic volumes from baseline to after RE treatment, however, was not statistically different between the groups ($P = 0.27$).

Portal Vein Diameter

Changes in portal vein diameter following RE is presented in Table 4. At baseline, no differences in portal vein diameters were observed between the two groups. In contrast to sequential lobar treatment, whole liver RE resulted in significantly increased portal vein diameters at 6 weeks (+16%) and 3 months (+17%) compared with baseline ($P < 0.05$). Additionally, portal vein diameter increase in the whole-liver treatment group was significantly higher than the sequential-lobar group at 6 weeks (+16% vs. +8%, $P = 0.031$) and 3 months (+17% vs. +6%, $P = 0.043$), respectively.

Table 5 Sequential lobar dynamics after treatment with sequential lobar ^{90}Y-radioembolization ($n = 17$)

Liver volumetry	ml	P value[a]
First liver lobe		
First RE	989 ± 438	
Second RE	898 ± 447 (−9%)	0.016
6 weeks	809 ± 482 (−18%)	0.002
3 months	896 ± 648 (−9%)	n.s.
Second liver lobe		
First RE	652 ± 416	
Second RE	738 ± 449 (+13%)	0.011
6 weeks	727 ± 415 (+11%)	n.s.
3 months	812 ± 464 (+25%)	0.046
Tumor volumetry		
First liver lobe		
First RE	163 ± 153	
Second RE	91 ± 92 (−44%)	0.024
Second liver lobe		
First RE	56 ± 66	
Second RE	89 ± 91 (+40%)	n.s.

n.s. not statistically significant

Data are means ± standard deviations and relative changes from baseline in percentages unless otherwise indicated

[a] Changes from baseline

Tumor Volume and Survival

Table 5 presents the change in tumor volume for patients treated in a sequential-lobar fashion. The mean tumor volume of the liver lobe scheduled for initial treatment was 163 ± 153 ml before radioembolization versus 56 ± 66 ml for the second treated liver lobe. At the time of the second RE, the tumor volume of the already treated liver lobe had decreased to 91 ± 92 ml ($P = 0.024$), whereas the mean tumor volume of the nontreated liver lobe had not changed significantly (89 ± 91 ml, $P > 0.05$).

For all patients, tumor load before RE was negatively correlated with post-RE overall survival (OS) ($r = -0.491$; $P = 0.003$).

As illustrated in Fig. 3, median survivals of the main group of colorectal cancer patients ($n = 22$) after whole liver RE and sequential lobar RE were not significantly different (9.8 months and 15.6 months respectively, $P = 0.293$) where for all patients, irrespective of the primary tumor entity, overall survival in the two different treatment groups were significantly different (9.7 months (whole liver) vs. 17.5 months (sequential), $P = 0.035$).

No complications due to extrahepatic seeding of the microspheres or procedure-related vascular complications were observed.

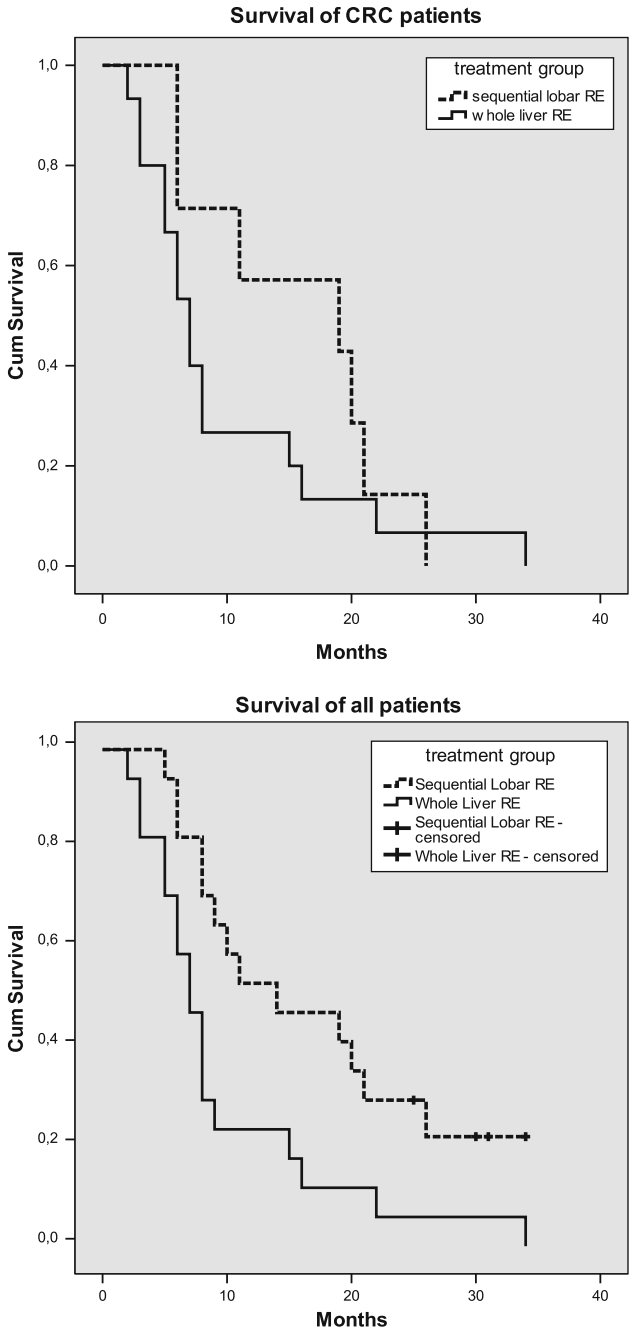

Fig. 3 Overall survival (OS) of patients (CRC only and all patients) treated with sequential-lobar and whole-liver ^{90}Y-radioembolization. OS of patients with colorectal liver metastases according to Kaplan–Meier method, whole-liver RE (mean OS: 9.8 months) versus sequential lobar RE (mean OS: 15.6 months), $P = 0.293$ and overall survival of all patients, whole-liver RE (mean OS: 9.7 months) versus sequential lobar RE (mean OS: 17.5 months), $P = 0.035$

Discussion

In ^{90}Y-radioembolization, the dose-limiting factor is excessive radiation exposure of liver parenchyma with resulting development of REILD. Typically, onset of

REILD is observed 4–8 weeks post-RE characterized by ascites and jaundice [12]. Pathophysiologically, REILD is consistent with VOD, comprising sinusoidal outflow obstruction through the development of reticulin fibers crisscrossing the sinusoidal and adjacent central venules, leading to a congestion of erythrocytes (Fig. 1) [25–27].

Response to ^{90}Y-radioembolization has been demonstrated to be dose-dependent [6]. However, in high-risk patients previously exposed to chemotherapies, increased bilirubin levels, low BMI, or young age, the incidence of REILD may increase to more than 20% if typical dosing schemes, such as the BSA model are applied [12]. No preventive measures, including protective drug prescriptions, have been described in the literature yet.

In 2004, ^{90}Y-radioembolization was administered to the whole liver using the BSA dosimetry model as recommended by the literature. However, a noticeable incidence (approximately 10% of treated cases) of significant liver impairment was observed in patients with advanced metastatic colorectal carcinoma and a history of numerous prior chemotherapies. Onset of liver function impairment after high-dose rate (HDR) brachytherapy of liver malignancies is not typically observed until several weeks posttherapy, with peak degradation after approximately 4–6 weeks and a recovery 3 months after radiation exposure [16, 17]. It was hypothesized that liver impairment similar to that for low-dose rate (LDR) brachytherapy was possible with ^{90}Y therapy. As a consequence, in 2008 sequential ^{90}Y-treatments of the left and right liver lobes were implemented with an interval of 6 weeks to allow functional recovery of the initially radioembolized liver lobe. This approach was intended to increase liver tolerance to radiation without reducing the total prescribed dose.

The experience described in this study suggests that sequential radioembolization of the left and right liver lobes provides increased liver tolerance to radiation compared with whole-liver treatment, thus mitigating potential radiation-induced compromise to normal liver. Compared with the sequential approach, patients with whole-liver embolization exhibited an increased likelihood of ascites and abnormal bilirubin.

Deferring treatment of the contralateral liver lobe for 6 weeks did not adversely affect survival in the (relative small) group of colorectal cancer patients (even showed a significant higher survival in the survival analysis of all patients irrespective of primary tumor site) and moreover resulted in less grade 3/4 toxicities after RE. This finding was supported by the fact that tumor volumes did not increase significantly in the untreated liver lobe during the intervening time interval before treatment of the second lobe. Thus, a sequentially performed radioembolization does not seem to have disadvantages compared with whole-liver radioembolization also from an oncological standpoint.

Although most treated patients did not show apparent significant compromise in liver function after RE, changes in lobar volume suggest that there may be localized liver injury and fibrosis. For patients who received sequential lobar treatment, a significant volume decrease (−9 and −18%) was observed in the first treated lobe at the second RE and 6 weeks after completion of RE, respectively. Conversely, a significant volume increase (+13 and +25%) was observed for the second treated lobe at the second RE and 3 months after completion of RE, respectively. Interestingly, volume decrease in both the first and second treated lobes (mean −14.7 and −1.9%) has been reported by Jakobs et al. following sequential lobar RE with glass microspheres [28]. However, for unilobar RE, these authors observed a similar result to the current study, with significant volume decrease (mean −14.3%) in the ipsilateral liver lobe, with significant hypertrophy (mean +20.3%) in the contralateral untreated lobe. The difference in results between the two studies may be due to the interval between imaging and volumetry before and after RE treatment. In the current study, post-RE imaging and volumes were calculated at 6 weeks and 3 months after the first RE, whereas in the Jakobs et al. study, post-RE imaging and lobar volumes were determined at a mean of 4.6 months after RE. Differences in post-RE imaging interval notwithstanding, volume decrease in the treated lobe likely represents radiation-induced fibrosis, with hypertrophy in the later treated lobe as a compensatory reaction of the radiation naïve parenchyma.

Increase in spleen volume and portal vein diameter after RE indicate the development of portal hypertension secondary to local liver injury with unfavorable results after whole liver RE. In the current study, significant increases in spleen volume after both whole-liver and sequential-lobar RE (28–64%) were observed. Corresponding increases in portal vein diameter (6–17%) also were noted with a significant higher increase in the whole-liver RE group (Table 4). These results are consistent with those reported by Jakobs et al. (3.9–5.4%).

Despite the fibrotic changes and portal hypertension noted after RE, there rarely appear to be resulting significant clinical effects in the sequentially treated group compared with the whole-liver treated group.

Some limitations apply to this study. First, patient cohorts were compared before and after modification of the treatment approach. To ensure that the learning curve involved with ^{90}Y-radioembolization did not influence results, patients treated before 2006 were excluded from the analysis. In the following years, at least 40 patients were treated annually. Second, this analysis is retrospective. However, inclusion was only allowed if patients had undergone a

thorough clinical follow-up program in our own institution, with complete data. Consequently, of 139 patients screened only 34 qualified for inclusion in this study. To avoid a potentially confounding impact of cirrhosis, all HCC patients were excluded. Nevertheless, a selection bias due to our strict eligibility criteria cannot be ruled out.

It also should be noted that the primary endpoint was not the development of REILD, which similar to radiation-induced liver disease (RILD) must be a symptomatic event per definition [12, 29, 30]. Instead clinical parameters that may indicate a considerable deterioration of liver function were chosen. However, ascites, bilirubin increase, and the development of portal hypertension are clear hallmarks of REILD, all of which were found more frequently in patients treated with whole-liver RE. In addition, REILD was found only in the group of patients who underwent whole-liver irradiation (3/17 patients, 18%) and not in patients who received the sequential approach.

Conclusions

Noncirrhotic patients who underwent sequential radioembolization of liver lobes at an interval of approximately 6 weeks may have fewer liver-related significant adverse events than patients who underwent whole-liver radioembolization. The sequential approach should be the preferred technique of ^{90}Y-radioembolization, at least in high-risk patients according to Sangro et al.

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Conflict of interest All authors disclose any actual or potential conflict of interest.

References

1. Wallace S, Carrasco CH, Charnsangavej C et al (1990) Hepatic artery infusion and chemoembolization in the management of liver metastases. Cardiovasc Intervent Radiol 13(3):153–160
2. Cosimelli M, Golfieri R, Cagol PP et al (2010) Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer 103(3):324–331
3. Gray B, Van Hazel G, Hope M et al (2001) Randomised trial of SIR-Spheres plus chemotherapy vs chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol 12(12):1711–1720
4. Mulcahy MF, Lewandowski RJ, Ibrahim SM et al (2009) Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer 115(9):1849–1858
5. Hilgard P, Hamami M, Fouly AE et al (2010) Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology 52(5):1741–1749
6. Kennedy A, Nag S, Salem R et al (2007) Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys 68(1):13–23
7. Nicolay NH, Berry DP, Sharma RA (2009) Liver metastases from colorectal cancer: radioembolization with systemic therapy. Nat Rev Clin Oncol 6(12):687–697
8. Sharma RA, van Hazel GA, Morgan B et al (2007) Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. J Clin Oncol 25(9):1099–1106
9. van Hazel GA, Pavlakis N, Goldstein D et al (2009) Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. J Clin Oncol 27(25):4089–4095
10. Salem R, Lewandowski RJ, Kulik L et al (2011) Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 140(2):497–507
11. Leung TW, Lau WY, Ho SK et al (1995) Radiation pneumonitis after selective internal radiation treatment with intraarterial ^{90}yttrium-microspheres for inoperable hepatic tumors. Int J Radiat Oncol Biol Phys 33(4):919–924
12. Sangro B, Gil-Alzugaray B, Rodriguez J et al (2008) Liver disease induced by radioembolization of liver tumors: description and possible risk factors. Cancer 112(7):1538–1546
13. Bianco JA, Appelbaum FR, Nemunaitis J et al (1991) Phase I–II trial of pentoxifylline for the prevention of transplant-related toxicities following bone marrow transplantation. Blood 78(5):1205–1211
14. Essell JH, Schroeder MT, Harman GS et al (1998) Ursodiol prophylaxis against hepatic complications of allogeneic bone marrow transplantation. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 128(12 Pt 1):975–981
15. Forrest DL, Thompson K, Dorcas VG et al (2003) Low molecular weight heparin for the prevention of hepatic veno-occlusive disease (VOD) after hematopoietic stem cell transplantation: a prospective phase II study. Bone Marrow Trans 31(12):1143–1149
16. Ricke J, Seidensticker M, Ludemann L et al (2005) In vivo assessment of the tolerance dose of small liver volumes after single-fraction HDR irradiation. Int J Radiat Oncol Biol Phys 62(3):776–784
17. Seidensticker M, Seidensticker R, Mohnike K et al (2011) Quantitative in vivo assessment of radiation injury of the liver using Gd-EOB-DTPA enhanced MRI: tolerance dose of small liver volumes. Radiat Oncol 6:40
18. Field KM, Dow C, Michael M (2008) Part I: liver function in oncology: biochemistry and beyond. Lancet Oncol 9(11):1092–1101
19. Deleporte A, Flamen P, Hendlisz A (2010) State of the art: radiolabeled microspheres treatment for liver malignancies. Expert Opin Pharmacother 11(4):579–586
20. Hermann RM, Rave-Frank M, Pradier O (2008) Combining radiation with oxaliplatin: a review of experimental results. Cancer Radiother 12(1):61–67
21. Rubbia-Brandt L, Audard V, Sartoretti P et al (2004) Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 15(3):460–466

22. Denecke T, Ruhl R, Hildebrandt B et al (2008) Planning transarterial radioembolization of colorectal liver metastases with Yttrium 90 microspheres: evaluation of a sequential diagnostic approach using radiologic and nuclear medicine imaging techniques. Eur Radiol 18(5):892–902
23. Seidensticker R, Denecke T, Kraus P et al (2011) Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol (in press)
24. Salem R, Lewandowski RJ, Gates VL et al (2011) Research reporting standards for radioembolization of hepatic malignancies. J Vasc Interv Radiol 22(3):265–278
25. Fajardo LF, Colby TV (1980) Pathogenesis of veno-occlusive liver disease after radiation. Arch Pathol Lab Med 104(11): 584–588
26. Bayraktar UD, Seren S, Bayraktar Y (2007) Hepatic venous outflow obstruction: three similar syndromes. World J Gastroenterol 13(13):1912–1927
27. DeLeve LD, Shulman HM, McDonald GB (2002) Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). Semin Liver Dis 22(1):27–42
28. Jakobs TF, Saleem S, Atassi B et al (2008) Fibrosis, portal hypertension, and hepatic volume changes induced by intra-arterial radiotherapy with ^{90}yttrium microspheres. Dig Dis Sci 53(9):2556–2563
29. Dawson LA, Normolle D, Balter JM et al (2002) Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys 53(4):810–821
30. Lawrence TS, Robertson JM, Anscher MS et al (1995) Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 31(5):1237–1248

Veröffentlichung 2

Interventional radiological procedures in the therapy for colorectal liver metastases.

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Radiologisch-interventionelle Verfahren zur Therapie von kolorektalen Lebermetastasen

Interventional Radiological Procedures in the Therapy for Colorectal Liver Metastases

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- interventional radiology
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- radiation oncology

Zusammenfassung

Mikrotherapeutische Verfahren in der interventionellen Radiologie stellen bei Inoperabilität (technische Inoperabilität, funktionelle Inoperabilität, Komorbiditäten, Wunsch des Patienten) neben der Chemotherapie eine Möglichkeit zur lokalen Kontrolle von Lebermetastasen dar. Einen Schwerpunkt stellen lokale Verfahren wie die Radiofrequenzablation oder die interstitielle Brachytherapie dar, bei denen unter Bildführung durch Ultraschall sowie CT- oder offene MRT-Systeme eine thermische bzw. radiogene Ablation der Malignome durchgeführt wird. Diese erweisen sich als sehr effektiv, sind dabei aber auf einen oligonodulären Befall limitiert. Zur Behandlung einer disseminierten Metastasierung haben sich lokoregionäre Techniken wie die Yttrium-90-Radioembolisation etabliert. Hier wird unter angiografischer Kontrolle der Wirkstoff in Form von radioaktiv markierten Mikrosphären über einen arteriellen Zugang appliziert. Dieser Artikel fokussiert sich auf Metastasen des kolorektalen Karzinoms als häufigste Tumorentität zur interventionell-radiologischen Therapie.

Abstract

Microtherapeutic procedures performed by interventional radiologists pose a viable alternative or additive to systemic chemotherapy for local tumour control in cases of non-operable (for technical, functional, and comorbidity reasons or at the patient's wish) liver metastases. A main focus includes local therapies such as radiofrequency ablation and interstitial brachytherapy which are performed under ultrasound, CT or MRI guidance to achieve a thermal or radiogenic ablation of the malignancy. Although highly effective, these procedures are limited to oligonodular manifestations. For disseminated metastases, locoregional techniques like the yttrium-90 radioembolisation have become established. Here, the active principle in the form of radioactively labelled microspheres is introduced into the liver through an arterial catheter under angiographic guidance. The present article focuses on metastases of colorectal cancer as the most frequent tumour entity encountered in interventional radiotherapy.

Bibliografie
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Einführung

Die Leber ist das häufigste Zielorgan einer hämatogenen, portalvenösen Metastasierung von gastrointestinalen Tumoren.

Dabei entstammt etwa die Hälfte der Lebermetastasen einem kolorektalen Karzinom (CRC). In vielen Fällen wird das Überleben durch die hepatische Metastasierung begrenzt; bei hepatisch metastasierten kolorektalen Karzinomen im natürlichen Verlauf finden sich exemplarisch über alle Stadien hinweg 1-Jahres-Überlebensraten bei lediglich einem Drittel der Patienten. Bei disseminiertem Befall (hepatisch und extrahepatisch) ergeben sich ohne Therapie noch deutlich geringere Überlebenszeiten [1, 2].

Als bislang einziges kurativ Verfahren gilt die chirurgische Resektion der Lebermetastasen, obwohl für bestimmte mikrotherapeutische Verfahren ein kurativ Potenzial diskutiert wird [3].

In potenziell kurativer Intention oder zum Erreichen einer Langzeitremission wird eine R0-Resektion angestrebt. Durch Resektion der Lebermetastasen kann ein 5-Jahres-Überleben zwischen 28 und 48 % der Patienten erreicht werden [4].

* Robert Damm und Ricarda Seidensticker haben gleichen Anteil an der Erstautorenschaft.

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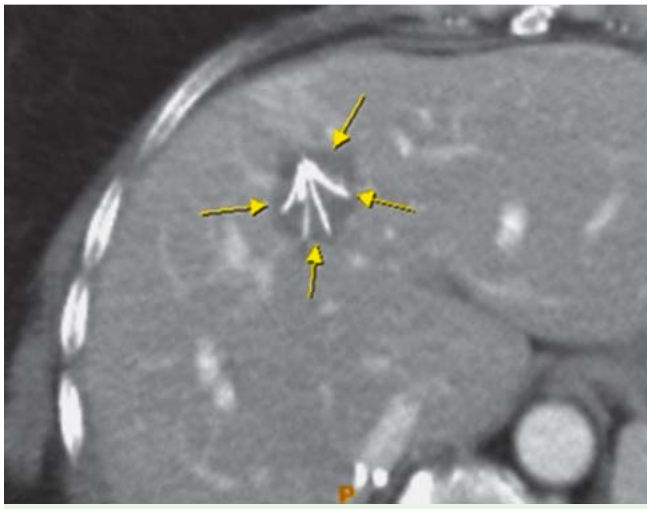

Abb. 1 Periinterventionelles CT: hypodens demarkierte Lebermetastase (Pfeile) mit einliegender Radiofrequenzsonde.

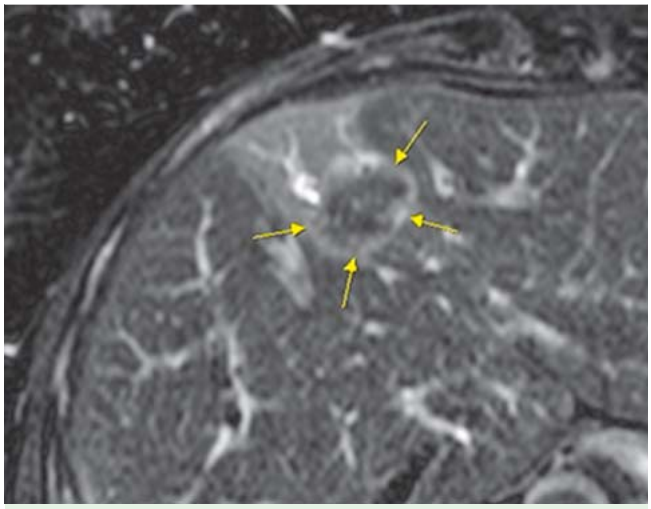

Abb. 2 Postinterventionelles MRT 3 Monate nach RFA: Residuelle Narbe (Pfeile) mit nachgeschalteter Begleitreaktion und leichtem perifokalen Ödem, angrenzend in der Peripherie leicht erweiterter Gallengang. In der weiteren Nachsorge zeigte sich eine anhaltende Remission (T2w mit Fettsuppression).

Nur für ein hoch selektioniertes Patientengut ermöglichen wiederholte Resektionen in der retrospektiven Auswertung ein 5-Jahres-Überleben von 73 % [5].

Viele Patienten mit hepatisch metastasiertem CRC zeigen jedoch ein intra- oder extrahepatisches Rezidiv im Verlauf nach R0-Resektion. Der initial kurative Therapieansatz kann somit nur für einen selektierten Anteil der Patienten dauerhaft erreicht werden [6].

Im Falle einer Irresektabilität (ca. ⅔ der Patienten mit kolorektalen Lebermetastasen) steht oftmals die systemische Chemotherapie im Vordergrund der Therapiebemühungen. Für das metastasierte kolorektale Karzinom ist die Therapie mit einer Kombination aus 5-Fluorouracil und Folinsäure mit Oxaliplatin oder Irinotecan der derzeitige Standard, der gegebenenfalls um Antikörper wie Bevacizumab ergänzt werden kann. Hiermit kann ein medianes Überleben von über 20 Monaten erreicht werden [7].

Als weiterer Zweig in der interdisziplinären Tumortherapie bieten die radiologisch-interventionellen Verfahren zahlreiche Möglichkeiten zur Tumorkontrolle in der Leber und können somit zur Verlängerung des Überlebens beitragen [8]. Speziell Patienten, die die Kriterien für eine Metastasenresektion initial oder im Verlauf nicht erfüllen oder deren Allgemeinzustand die weitere Anwendung von Zytostatika limitiert, können von den durch niedrige Mortalität und Morbidität charakterisierten minimalinvasiven Verfahren profitieren [9].

Aufgrund der allgemeinen Verbreitung wird in diesem Artikel als Entität das kolorektale Karzinom thematisiert. Dabei möchte dieser Artikel den Lesern unter den zahlreichen radiologischen Verfahren die Radiofrequenzablation (RFA), weitere lokale Verfahren wie die laserinduzierte Thermotherapie (LITT), die interstitielle Brachytherapie sowie die Radioembolisation (RE) vorstellen und die vorliegenden Studienergebnisse (**Tab. 1**) kritisch diskutieren. Erwähnung finden ebenfalls die Nebenwirkungen dieser Therapien.

Lokale Verfahren

Radiofrequenzablation

Die Radiofrequenzablation (RFA) ist einerseits als intraoperativ eingesetztes Verfahren etabliert und stellt andererseits das aktuell verbreitetste radiologisch-interventionelle Verfahren zur perkutanen Ablation von Lebermetastasen dar. In beiden Anwendungen wird äquivalent zur chirurgischen Resektion eine vollständige Eliminierung der Tumorzellen angestrebt.

Bei der RFA wird mittels Applikation von Wechselströmen im Gewebe eine Hyperthermie mit folgender Koagulationsnekrose erzeugt, die auf eine Größe von bis zu 5 cm ausgedehnt werden kann, wobei durch Umpositionierung der Nadel eine größere Ablationszone erreicht werden kann [28]. Zur kompletten Ablation wird ein Sicherheitssaum von 1 cm um den Tumor eingeschlossen. Die Deutsche Gesellschaft für Interventionelle Radiologie und minimal-invasive Therapie empfiehlt einen maximalen Tumordurchmesser von 3,5 cm zur sicheren Ablation bei multifokaler Metastasierung sowie bei einem unifokalen Herd einen maximalen Durchmesser von 5 cm mit 7 cm messender Ablationszone [29]. Um mit einer Resektion vergleichbare Ergebnisse zu erreichen, ist nach aktuellen Studien eine maximale Metastasengröße von 3 cm empfehlenswert [30].

Limitationen des Verfahrens sind vor allem Kühlungseffekte durch benachbarte Gefäße, die begrenzte Größe der induzierten Koagulationsnekrose und die Hitzevulnerabilität angrenzender Strukturen (Gallengänge etc.).

Die RFA kann perkutan sowohl unter sonografischer Bildführung als auch CT- oder MRT-gestützt angewendet werden. Nachteil der Sonografie ist hierbei die Bildempfindlichkeit gegenüber der wärmebedingten Gasbildung im Verlauf der Ablation und die schlechte Darstellbarkeit tieferer Leberabschnitte [31]. Hier zeigt sich ein Vorteil der fluoroskopischen Nadelplatzierung und Ablation in der Computertomografie [32]. Die Anwendung in der offenen MRT bietet darüber hinaus das simultane Monitoring der Temperaturentwicklung und die multiplanare Darstellung der Applikatoren, die eine optimale Platzierung erlaubt [33]. Ein Beispiel einer bildgeführten Radiofrequenzablation und Nachsorge 3

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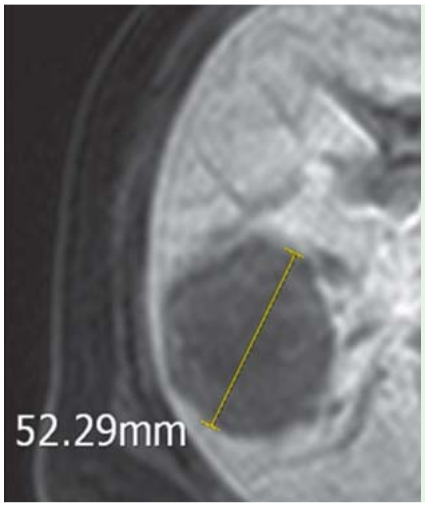

Abb. 3 MRT vor interstitieller Brachytherapie: Metastase eines kolorektalen Karzinoms > 5 cm (T1w GRE mit leberspezifischem Kontrastmittel Gd-EOB-DTPA in der hepatobiliären Phase 20 min nach Applikation).

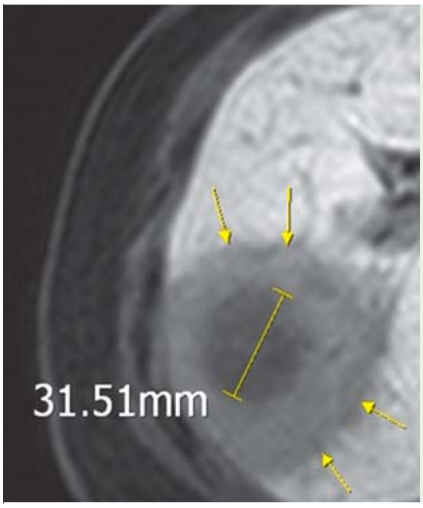

Abb. 4 MRT 3 Monate nach Brachytherapie: residuelle Nekrose der Metastase ~ 3 cm deutlich hypointens (Messlinie), umgebende Strahlenreaktion mit strahleninduziertem Funktionsausfall des Leberparenchyms (fehlende Aufnahme des hepatozytenspezifischen Kontrastmittels Gd-EOB-DTPA, Pfeile).

Monate postinterventionell findet sich in **Abb. 1** sowie **Abb. 2**.

Die klinische Anwendung ist bisher in vielen Studien evaluiert, jedoch finden sich häufig monozentrische Erfahrungen ohne Vergleichsarme. Darüber hinaus ist eine Stratifizierung nach begleitenden oder folgenden Therapien im Beobachtungszeitraum schwierig.

Für die intraoperative, ultraschallgestützte Ablation bei teils größeren Läsionen findet sich ein medianes Überleben von 24 bis 29 Monaten bei großen Fallzahlen. Nach der radiologisch-interventionellen, perkutanen RFA sind bedingt vergleichbare Ergebnisse von 28 bis 36 Monaten dokumentiert, wobei diese Daten bei meist nicht resektablen Patienten erhoben wurden und eine negative Selektion vermutet werden darf [10, 12–14].

Als Komplikationen der Radiofrequenzablation sind hitzeinduzierte Effekte auf benachbarte Organstrukturen zu nennen, u. a. Gallengangsstenosen, arteriovenöse Fisteln und Gefäßthrombosen. Daneben können alle typischen Ereignisse infolge einer Leberpunktion auftreten, darunter Blutungen und Infektionen. Die Häufigkeit der diesbezüglichen Majorkomplikationen wird mit 1,9–6% angegeben. Eine spezielle Form der Nebenwirkung ist das Postablationssyndrom, welches bei etwa einem Drittel der Ablationen mit Fieber, Schwindel und Schmerzen nach 3 bis 5 Tagen auftritt. Als weitere Problematik wird die Induktion von Stichkanalmetastasen (Häufigkeit ca. 2,7% in Abhängigkeit von der Tumorentität) diskutiert [34].

Laserinduzierte Thermotherapie und weitere lokalablative Verfahren

Bei der LITT wird durch Nd:YAG-Laser mit einer Wellenlänge von 1064 nm eine Hyperthermie erzeugt [35], die identisch zur Radiofrequenzablation wirkt und ebenso in der MR-Bildgebung überwacht werden kann [16]. Das Verfahren wurde insbesondere zur Anwendung im Kernspintomografen konzipiert, da anfangs keine MR-kompatiblen RFA-Sonden zur Verfügung standen und nur mit dieser Methode der erhöhte Weichteilkontrast und die Möglichkeit der Onlinethermometrie der MRT genutzt werden konnte.

Mit der laserinduzierten Thermotherapie können zirkuläre Nekrosen mit einem Durchmesser von bis zu 5 cm (in Multiapplikatortechnik Erweiterung der Ablationszone bzw. Optimierung der Ablationsgeometrie möglich) erzeugt werden und der therapeutische Ansatz unterliegt damit denselben Beschränkungen wie denen der RFA (größere Tumoren, Nähe von kühlenden Gefäßen oder hitzesensibler Strukturen) sowie ebenfalls vergleichbaren Komplikationen bei etwa 2,2% der Patienten [35]. Nachteile der LITT sind die recht hohen Anschaffungskosten der Lasergeneratoren und die preisintensiven Applikatoren und Laserfasern.

Vor dem Hintergrund des Heat-Sink-Effekts könnte die Mikrowellenablation (MWA) eine geeignete Alternative zu LITT und RFA darstellen, da hierbei die Nachbarschaft zu größeren Gefäßen technisch nicht limitierend ist und gleichzeitig größere Ablationsvolumina möglich sind [36].

Für die laserinduzierte Thermotherapie sind zur Radiofrequenzablation vergleichbare 1-Jahres-Überlebensraten von über 90% an großen Patientenkollektiven publiziert, nach 5 Jahren leben jeweils noch ungefähr ein Drittel der Patienten. Das mediane Überleben ist mit 23 bis 42 Monaten angegeben [16, 18].

Obwohl noch nicht an größeren Patientenzahlen für das kolorektale Karzinom validiert, sind auch nach der Mikrowellenablation 5-Jahres-Überlebensraten von bis zu 32% möglich [37].

Ein weiteres vielversprechendes Verfahren stellt die irreversible Elektroporation dar. Bei dieser wird über eine Stromapplikation die Zellmembran der Zellen geschädigt und somit der Zelltod induziert. Erste klinische Untersuchungen zeigen sowohl die Machbarkeit als auch Verträglichkeit zur Ablation von Lebermetastasen [38]. Bisher fehlen jedoch Langzeiterfahrungen hinsichtlich der lokalen Kontrolle, des Überlebens und möglicher Komplikationen.

Interstitielle Brachytherapie

Als weiteres perkutan durchgeführtes Interventionsverfahren kann die Brachytherapie zur Tumormassereduktion und vollständigen Ablation bei Lebermetastasen eingesetzt werden, die aufgrund ihrer Größe nicht mehr einer RFA zugänglich sind. Darüber hinaus ergeben sich bei diesem Verfahren keine Einschränkungen durch Kühlungseffekte benachbarter Gefäße. Neben dem intraoperativen Einsatz (IORT) können unter Kontrolle durch CT- oder offene MRT-Systeme Bestrahlungskatheter in die Leberherde eingelegt werden. Nach Erstellen eines Planungs-CT/-MRT mit den einliegenden Kathetern erfolgt die Bestrahlungsplanung und anschließend die computergestützte Bestrahlung mittels einer Iridium-192-Quelle in Afterloading-Technik. Die bildgeführte Durchführung mittels CT oder MRT erlaubt hierbei eine komplikationsarme und genauere Katheterplatzierung und Bestrahlungsplanung im Vergleich zur intraoperativen Anwendung [39]. Gegenüber der perkutanen Bestrahlung mittels Teletherapie

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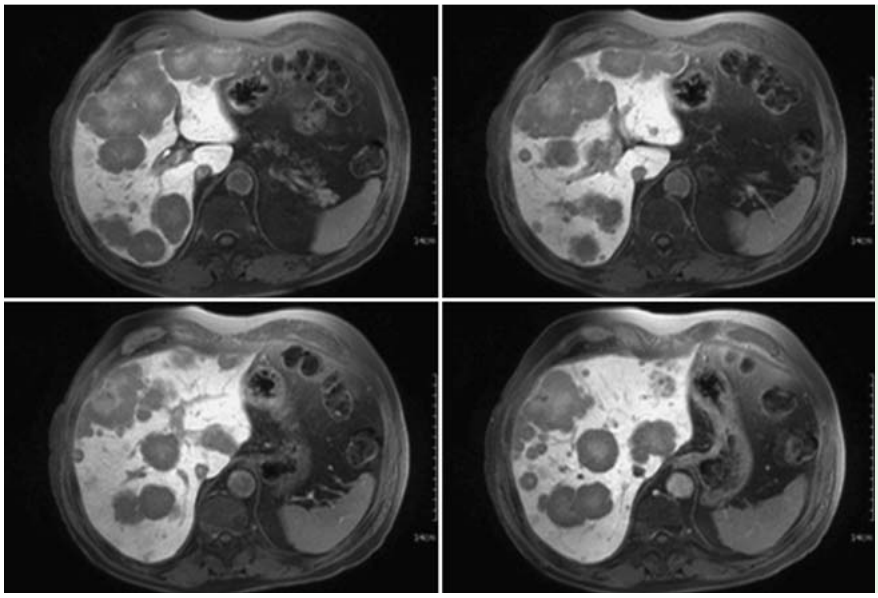

Abb. 5 MRT vor Radioembolisation: Ausgedehnte bilobäre Lebermetastasierung (T1w GRE mit Gd-EOB-DTPA in der hepatobiliären Phase).

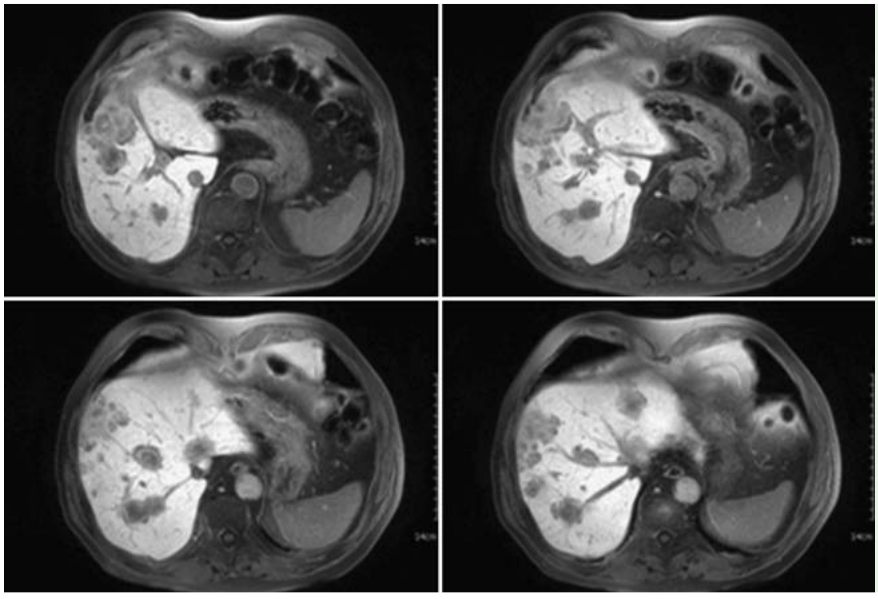

Abb. 6 MRT 3 Monate nach Radioembolisation: Partielle Remission der Lebermetastasen (T1w GRE mit Gd-EOB-DTPA in der hepatobiliären Phase).

weist die interstitielle Brachytherapie zudem den Vorteil einer festen Platzierung der Strahlenquelle im Tumor ohne Beeinflussung durch Atemexkursionen auf [40]. Zur effektiven Ablation wird eine tumorumschließende Zieldosis von minimal 20 Gy angestrebt, wobei in den zentraleren Tumoranteilen sehr viel höhere Dosen erreicht werden [41].

Mit dem Verfahren der CT-gestützten Brachytherapie konnte für intensiv vortherapierte Patienten mit fortgeschrittener hepatischer Metastasierung eines kolorektalen Karzinoms (Größe 1,0–13,5 cm Durchmesser; medianer Diameter: 5 cm) ein medianes Überleben von 23,4 Monaten aufgezeigt werden [21]. Anzumerken ist, dass die beobachteten Patienten einer negativen Selektion gegenüber den thermischen Verfahren unterliegen.

Die möglichen Komplikationen der Brachytherapie werden aktuell langzeitig untersucht, bislang noch nicht publizierte Daten zeigen eine Rate von 2,4% an Majorkomplikationen. Neben den Punktionsrisiken durch teils mehrere Bestrahlungskatheter (Blutungen, Leberabszesse oder peritoneale Infektionen) ist vor allem eine strahleninduzierte, doch meist subklinische Schädigung des umliegenden Leberparenchyms zu beobachten, die durchschnittlich 6 Wochen nach der Therapie als verminderte Aufnahme hepatozytenspezifischer Kontrastmittel auffällt und die residuelle, häufig nekrotische Metastase umgibt [42].

Abb. 3 und **4** zeigen als Beispiel eine präinterventionelle Lebermetastase sowie das Ansprechen 3 Monate nach der Therapie (nekrotische Metastase mit umgebender radiogener Schädigung des Leberparenchyms).

Lokoregionäre Verfahren

Yttrium-90-Radioembolisation

Bei der Yttrium-90-Radioembolisation handelt es sich um ein Verfahren zur Behandlung disseminierter hepatischer Malignome, bei dem ein radioaktives Isotop, in diesem Falle ^{90}Y, gebunden an Kunstharz- oder Glasmikrosphären, mittels eines Kathe-

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Tab. 1 Langzeitergebnisse nach interventioneller Therapie kolorektaler Lebermetastasen.

Autor	Pat.-Anzahl	Metastasen Anzahl	Metastasen Größe (cm)	Ergebnisse medianes Follow-up (m)	Ergebnisse lokale Kontrolle (%)	Ergebnisse Überlebensrate (%), (0,5/1/5y)	Ergebnisse Median OS (m)	Ergebnisse Median PFS (m)
Radiofrequenzablation								
Solbiati et al. 2001 [10]	117	179	0,9–9,6	6–52	61	–/93/–	36	12
Gillams et al. 2005 [11]	167	1–27 p. P.	1–12	–	–	–/91/25	31	–
Berber et al. 2005 [12]*	135	1–12 p. P.	1,2–10,2	–	–	–	28,9	–
Siperstein et al. 2007 [13]**	234	292	< 10,2	24	–	–/–/18	24	–
Gillams et al. 2009 [14]	309	n < 5 p. P.	< 5	–	–	–/–/18	28	–
		n > 5 p. P.	> 5	–	–	–/–/3	14	–
Sofocleous et al. 2011 [15]	56	71	0,5–5,7	–	–	–/91/–	31	–
LITT								
Mack et al. 2001 [16]	393	1 203	< 5	> 18	–	97/93/30	42	–
Vogl et al. 2004 [17]	603	1 801	< 5	> 18	–	–/94/37	35	–
Pech et al. 2007 [18]	66	117	< 5	8,7	–	–/–/–	23	6,1
Mikrowellenablation##								
Morita et al. 2004 [19]	52	–	–	–	–	–/–/20–24	–	–
Ogata et al. 2008 [20]	50	–	2,1	33	–	–/–/32	–	–
interstit. Brachytherapie								
Ricke et al. 2010 [21]	73	199	1–13,5	41	75	–	23,4	6
Radioembolisation		**Tumorlast**						
Stubbs et al. 2006 [22]***	80	–		3	83	–	–	–
Kennedy et al. 2006 [23]	208	–		13	–	–	10,5#	–
Jakobs et al. 2008 [24]	41	–		–	–	–	10,5	–
Cosimelli et al. 2010 [25]	50	< 25–50 %		11	–	–/50/–	12,6	3,7
Seidensticker et al. 2011 [26]	29	20–50 %		–	–	–	8,3	5,5
Kosmider et al. 2011 [27]***	19	–		18,6	–	–	29,4	10,4

* laparoskopische RFA; ** laparoskopische RFA nach Hemihepatektomie; *** Kombinationsregime mit Chemotherapie (5-FU intraarteriell o. systemisch); # Überlebensangabe nur für Therapieresponder; ## gemischte Kollektive mit offener/perkutaner MWA bzw. MWA und RFA, aus Boutros et al. 2010 [37]; OS: Overall survival; PFS: progressionsfreies Überleben.

ters in die leberversorgenden Arterien appliziert wird. Die Katheterpositionierung erfolgt dabei mittels digitaler Subtraktionsangiografie über einen transfemoralen Zugang. Maligne Prozesse der Leber werden bis zu 90 % über Arterien versorgt, während gesundes Leberparenchym hauptsächlich über die V. portae den Blutzustrom erhält [43]. Damit kann durch die Radioembolisation sowohl die Blutversorgung von Tumoren unterbunden werden als auch eine Bestrahlung derselben durchgeführt werden.

Vor der Therapie wird eine digitale Subtraktionsangiografie zur Beurteilung der Gefäßsituation der Leber durchgeführt. Kollaterale Arterien, die einen potenziellen extrahepatischen Abstrom der applizierten Mikrosphären in den Gastrointestinaltrakt ermöglichen, werden dabei mittels thrombogener Metallspiralen (Coils) verschlossen [44]. Anschließend wird 99-mT-markiertes makroaggregiertes Albumin in die Leber appliziert, um in einer nachfolgenden Szintigrafie eine Anreicherung im extrahepatischen Oberbauch auszuschließen und den Leber-Lungen-Shunt für die Dosisberechnung zu quantifizieren [45]. Erst wenn diese Simulation erfolgreich verläuft, kann in einer weiteren Sitzung das therapeutisch wirksame Radioembolisat appliziert werden.

In der ersten prospektiven Evaluation dieses Verfahrens als Monotherapie bei Patienten mit fortgeschrittenem, hepatisch metastasiertem kolorektalen Karzinom und weitestgehend ausgeschöpften Therapieoptionen zeigte sich ein medianes Gesamtüberleben von 12,6 Monaten, das 2-Jahres-Überleben erreichte ein Fünftel der eingeschlossenen Patienten [25]. Gray et al. zeigten in einer randomisierten Studie, in der die Radioembolisation in Kombination mit einer intraarteriell applizierten Chemotherapie mittels Floxuridin angewendet wurde, ein 2-Jahres-Überleben von 39 % gegenüber 29 % nach alleiniger Chemotherapie [46].

Das Beispiel einer disseminierten Lebermetastasierung zeigen **Abb. 5** vor der Radioembolisation und **Abb. 6** in der Nachsorge nach 3 Monaten.

Aufgrund der Anwendung in interdisziplinären Therapiekonzepten ist die Bewertung der erreichten Endpunkte schwierig und es fehlen Daten zur alleinigen Effektivität der Radioembolisation. In der Salvage-Situation kann ein medianes Überleben von 8 bis 12 Monaten erreicht werden im Vergleich zu Best Supportive Care (BSC), worunter nur 3,5 Monate zu verzeichnen sind [23, 24, 26]. Kommt die Yttrium-90-Radioembolisation jedoch in einem früheren Krankheitsstadium in Kombination mit einer systemischen Chemotherapie zum Einsatz, sind Überlebenszeiten bis zu 30 Monate möglich [27]. In einem großen multizentrischen Studienrahmen wird aktuell prospektiv-randomisiert die Wirksamkeit der Yttrium-90-Radioembolisation in Kombination mit FOLFOX als Erstlinientherapie untersucht.

Obwohl mit einer geringen Morbidität assoziiert, zeigen sich bei der Radioembolisation zumeist subklinische strahleninduzierte Leberfunktionsstörungen, besonders wenn die gesamte Leber in einer Therapiesitzung behandelt wird. Zu den schwereren Komplikationen zählen neben Pleuraergüssen vor allem Aszites, Bilirubinerhöhung sowie Ikterus, die unter der Bezeichnung der „radioembolization-induced liver disease“ zusammengefasst werden und mit einer Häufigkeit von etwa 10 % auftreten und durch eine zweiseitige Therapie der Leber weiter gesenkt werden können [47]. Größere Komplikationen durch die katheterangiografische Technik sind bei sorgfältiger Durchführung dagegen nicht zu erwarten.

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Diskussion

Die minimalinvasive interventionell-radiologische Therapie kolorektaler Lebermetastasen zielt auf eine möglichst belastungsarme Behandlung des Patienten bei hoher Effektivität. Dabei bietet sie für verschiedene Tumorkonfigurationen eine geeignete Methode von perkutan interstitieller Ablation eines oligonodulären Befalls bis zur Therapie einer diffusen hepatischen Filiarisierung über den transarteriellen Zugang. Nachteilig mag die lokale bzw. lokoregionäre Begrenzung der Therapie erscheinen, doch die häufig prognostisch führende Lebermetastasierung kann oftmals gut kontrolliert werden.

Bestehen keine Kontraindikationen für eine chirurgische Resektion, gilt diese unverändert als Goldstandard und wird allgemein präferiert, obwohl der potenziell kurative Charakter für viele Patienten oftmals nicht langfristig besteht. Unbestritten ist dabei die Prognoseverbesserung durch die R0-Resektion [48]. Mit den neueren Verfahren der atypischen Resektion können immer mehr Patienten einer operativen Therapie zugeführt werden, jedoch wurden hierbei in einer großen Studie nahezu 10% an R1-Resektionen nachgewiesen [49]. Dem vergleichbar sind die Lokalrezidivquoten nach Radiofrequenzablation mit 3,6 bis 16% (Metastasen < 3 cm) [50,51].

Das 5-Jahres-Überleben nach bildgeführter Radiofrequenzablation bei kolorektalen Lebermetastasen kann bis zu 33% betragen und ist mit den Überlebensraten in den bereits genannten chirurgischen Konzepten durchaus vergleichbar, wobei es zu beachten gilt, dass es sich bei der RFA hier um selektierte Patientenkollektive handelt (< 3 Tumoren; Diameter: < 3,5 cm) [14]. Die laparoskopisch durchgeführte Radiofrequenzablation zeigt zudem ähnliche Ergebnisse, wobei die operativ durchgeführte RFA in der Regel einer positiven Patientenselektion unterliegt [12,52]. Hier lässt sich auch feststellen, dass weder die Tumoranzahl (< oder > 3) noch das Vorliegen extrahepatischer Manifestationen einen Einfluss auf das Überleben haben. Nur der maximale Durchmesser der dominanten Läsion < 3 cm ist als prognostisch positiv zu bewerten [12].

Eine Metaanalyse von 7 nicht randomisierten Studien bei solitären Lebermetastasen zeigte wiederum einen signifikanten Überlebensvorteil für die Patienten mit hepatischer Resektion im Vergleich zur RFA, weshalb die Empfehlung bei Operabilität weiterhin zur Resektion geht [53].

Ein weiterer interessanter Ansatz ist das „Test-of-time"-Verfahren, bei dem potenziell kurativ zu resezierende Lebermetastasen zunächst einer bildgeführten Radiofrequenzablation unterzogen werden und die Operation ca. 6–12 Wochen später im extra- und intrahepatisch rezidivfreien Intervall geplant ist. Studien zeigen, dass 70% der Patienten innerhalb des Beobachtungszeitraums vor der geplanten Operation einen extra- oder intrahepatischen Progress außerhalb der therapierten Läsion aufwiesen, wodurch festzustellen ist, dass diese Patienten wahrscheinlich nicht von einer initialen Resektion nachhaltig profitiert hätten [54,55].

Perspektivisch sind die Anwendungen der Radiofrequenzablation über den bisher rein palliativen Charakter hinaus durchaus denkbar und als Alternative oder zusätzlich zur chirurgischen Resektion vorstellbar [56].

Die laserinduzierte Thermotherapie zeigt bei ähnlicher Indikation vergleichbare Ergebnisse, wobei gesagt werden muss, dass hierzu keine prospektiven Analysen vorliegen. Auch die Mikrowellenablation mit ihren Vorteilen hinsichtlich der Unabhängigkeit von Kühlungseffekten und Größenlimitationen schafft zur RFA vergleichbare Resultate mit einem 5-Jahres-Überleben bis 32%, doch sind bisher teils Patientenkollektive zusammen mit der RFA und insgesamt keine größeren Fallzahlen für das kolorektale Karzinom publiziert [37].

Wenn speziell die Tumorgröße oder -lokalisation die thermoablativen Verfahren technisch limitiert, stellt die interstitielle Brachytherapie eine lohnende Erweiterung des interventionell-radiologischen Spektrums dar und wird in enger Zusammenarbeit mit einem Strahlentherapeuten in Afterloading-Technik durchgeführt. Für Lebermetastasen bis zu 13,5 cm Durchmesser kann mit der interstitiellen Brachytherapie eine lokale Kontrolle bei 75% der Läsionen erreicht werden (Zieldosis: 15–25 Gy). In einer Subgruppenanalyse zeigte sich eine signifikant bessere Kontrolle von 84%, wenn tumorumschließend eine Dosis von mindestens 20 Gy appliziert wird. Auch Patienten mit größeren Tumorvolumina (> 5 cm) zeigten ein zur thermoablativen Therapie vergleichbares medianes Überleben von 23,4 Monaten [21].

Auch bei Vorliegen einer multifokalen, diffusen Metastasierung kann die radiologische Mikrotherapie eine wertvolle Ergänzung zur oftmals belastenden systemischen Chemotherapien darstellen, indem mit Verfahren wie z. B. der Yttrium-90-Radioembolisation mit geringem Morbiditätsrisiko Tumormassen reduziert oder zumindest kontrolliert werden können. Zugute kommt dabei die hohe Dosis, die am Tumor erreicht werden kann und auch bei chemorefraktären Tumoren noch eine Wirksamkeit aufweist. Die besten Ergebnisse konnten dennoch dann gezeigt werden, wenn Verfahren wie die Radioembolisation in einem frühen Stadium synergistisch mit einer systemischen oder intraarteriellen Chemotherapie zur Anwendung kommen [22,27].

Aber auch in der Salvage-Therapie profitieren Patienten von der Radioembolisation, wie in zahlreichen Studien gezeigt wurde [23,24,26].

Zudem sind in jüngerer Zeit die ersten Studien zur Anwendung der transarteriellen Chemoembolisation mit zytostatikabeladenen Embolisationspartikeln (z. B. Irinotecan) veröffentlicht, erste Phase-II-Studien zeigen ein gutes Ansprechen mit einem medianen Überleben von 25 Monaten beim leberdominant metastasierten kolorektalen Karzinom. Jedoch fehlen auch hier randomisierte Studien mit einem Vergleich zu etablierten systemischen Therapien [57].

Unbefriedigend bleibt die insgesamt unzureichende Evidenzlage bei den meisten interventionellen Verfahren, weshalb die Durchführung kontrollierter randomisierter Studien kurzfristiges Ziel für die verschiedenen Methoden sein sollte.

Ein abschließender Aspekt sollte die interdisziplinäre Zusammenarbeit der onkologisch tätigen Fachrichtungen sein, von der Patienten mit Lebermetastasen deutlich profitieren können. Neben der engen Verflechtung von chirurgischer Resektion und systemischer Therapie zeigt sich auch beispielsweise in der Kombination von der Radiofrequenzablation mit der Resektion oder Chemotherapie ein den jeweils einzelnen Modalitäten überlegenes Gesamtüberleben [58]. Dies wird ebenfalls in der Kombination aus systemischer Therapie und wiederholten interstitiellen Brachytherapien deutlich [21].

Interessenkonflikt: Nein

Literatur

1 *Cady B, Monson DO, Swinton NW.* Survival of patients after colonic resection for carcinoma with simultaneous liver metastases. Surg Gynecol Obstet 1970; 131: 697–700
2 *Wood CB, Gillis CR, Blumgart LH.* A retrospective study of the natural history of patients with liver metastases from colorectal cancer. Clin Oncol 1976; 2: 285–288

Heruntergeladen von: Medizinische Fakultät der Universität Magdeburg. Urheberrechtlich geschützt.

3 *Hompes D, Prevoo W, Ruers T.* Radiofrequency ablation as a treatment tool for liver metastases of colorectal origin. Cancer Imaging 2011; 11: 23–30
4 *Ito K, Govindarajan A, Ito H et al.* Surgical treatment of hepatic colorectal metastasis: evolving role in the setting of improving systemic therapies and ablative treatments in the 21st century. Cancer J 2010; 16: 103–110
5 *Andreou A, Brouquet A, Abdalla EK et al.* Repeat hepatectomy for recurrent colorectal liver metastases is associated with a high survival rate. HPB (Oxford) 2011; 13: 774–782
6 *Khatri VP, Petrelli NJ, Belghiti J.* Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? J Clin Oncol 2005; 23: 8490–8499
7 *Goldberg RM, Sargent DJ, Morton RF et al.* A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004; 22: 23–30
8 *Yothers G.* Toward progression-free survival as a primary end point in advanced colorectal cancer. J Clin Oncol 2007; 25: 5153–5154
9 *Sutherland LM, Williams JA, Padbury RT et al.* Radiofrequency ablation of liver tumors: a systematic review. Arch Surg 2006; 141: 181–190
10 *Solbiati L, Livraghi T, Goldberg SN et al.* Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. Radiology 2001; 221: 159–166
11 *Gillams AR, Lees WR.* Radiofrequency ablation of colorectal liver metastases. Abdom Imaging 2005; 30: 419–426
12 *Berber E, Pelley R, Siperstein AE.* Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. J Clin Oncol 2005; 23: 1358–1364
13 *Siperstein AE, Berber E, Ballem N et al.* Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. Ann Surg 2007; 246: 559–565
14 *Gillams AR, Lees WR.* Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. Eur Radiol 2009; 19: 1206–1213
15 *Sofocleous CT, Petre EN, Gonen M et al.* CT-guided radiofrequency ablation as a salvage treatment of colorectal cancer hepatic metastases developing after hepatectomy. J Vasc Interv Radiol 2011; 22: 755–761
16 *Mack MG, Straub R, Eichler K et al.* Percutaneous MR imaging-guided laser-induced thermotherapy of hepatic metastases. Abdom Imaging 2001; 26: 369–374
17 *Vogl TJ, Straub R, Eichler K et al.* Colorectal carcinoma metastases in liver: laser-induced interstitial thermotherapy–local tumor control rate and survival data. Radiology 2004; 230: 450–458
18 *Pech M, Wieners G, Freund T et al.* MR-guided interstitial laser thermotherapy of colorectal liver metastases: efficiency, safety and patient survival. Eur J Med Res 2007; 12: 161–168
19 *Morita T, Shibata T, Okuyama M et al.* [Microwave coagulation therapy for liver metastases from colorectal cancer]. Gan To Kagaku Ryoho 2004; 31: 695–699
20 *Ogata Y, Uchida S, Hisaka T et al.* Intraoperative thermal ablation therapy for small colorectal metastases to the liver. Hepatogastroenterology 2008; 55: 550–556
21 *Ricke J, Mohnike K, Pech M et al.* Local response and impact on survival after local ablation of liver metastases from colorectal carcinoma by computed tomography-guided high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 2010; 78: 479–485
22 *Stubbs RS, O'Brien I, Correia MM.* Selective internal radiation therapy with 90Y microspheres for colorectal liver metastases: single-centre experience with 100 patients. ANZ J Surg 2006; 76: 696–703
23 *Kennedy AS, Coldwell D, Nutting C et al.* Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. Int J Radiat Oncol Biol Phys 2006; 65: 412–425
24 *Jakobs TF, Hoffmann RT, Dehm K et al.* Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. J Vasc Interv Radiol 2008; 19: 1187–1195
25 *Cosimelli M, Golfieri R, Cagol PP et al.* Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer 2010; 103: 324–331
26 *Seidensticker R, Denecke T, Kraus P et al.* Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol 2011; 35: 1066–1073
27 *Kosmider S, Tan TH, Yip D et al.* Radioembolization in combination with systemic chemotherapy as first-line therapy for liver metastases from colorectal cancer. J Vasc Interv Radiol 2011; 22: 780–786
28 *Pereira PL, Trubenbach J, Schmidt D.* Radiofrequency ablation: basic principles, techniques and challenges. Rofo 2003; 175: 20–27
29 *Pereira PL.* Perkutane bildgesteuerte Leber-Tumortherapie mittels Radiofrequenz-Ablation (RFA). Deutsche Gesellschaft für Interventionelle Radiologie und minimal-invasive Therapie 2012. Im Internet: http://v2.degir.de/download/dokman/Leitlinie-RFA; Stand 9.2.2012
30 *Kim KH, Yoon YS, Yu CS et al.* Comparative analysis of radiofrequency ablation and surgical resection for colorectal liver metastases. J Korean Surg Soc 2011; 81: 25–34
31 *Jung EM, Clevert DA, Rupp N.* Contrast-enhanced ultrasound with Optison in percutaneous thermoablation of liver tumors. Rofo 2003; 175: 1403–1412
32 *Stroszczynski C, Gretschel S, Gaffke G et al.* [Laser-induced thermotherapy (LITT) for malignant liver tumours: the role of sonography in catheter placement and observation of the therapeutic procedure]. Ultraschall Med 2002; 23: 163–167
33 *Rempp H, Clasen S, Pereira PL.* Image-based monitoring of magnetic resonance-guided thermoablative therapies for liver tumors. Cardiovasc Intervent Radiol 2011 Jul 22 [Epub ahead of print]
34 *Nemcek AA.* Complications of radiofrequency ablation of neoplasms. Semin Intervent Radiol 2006; 23: 177–187
35 *Vogl TJ, Straub R, Zangos S et al.* MR-guided laser-induced thermotherapy (LITT) of liver tumours: experimental and clinical data. Int J Hyperthermia 2004; 20: 713–724
36 *Simon CJ, Dupuy DE, Iannitti DA et al.* Intraoperative triple antenna hepatic microwave ablation. AJR Am J Roentgenol 2006; 187: W333–W340
37 *Boutros C, Somasundar P, Garrean S et al.* Microwave coagulation therapy for hepatic tumors: review of the literature and critical analysis. Surg Oncol 2010; 19: e22–e32
38 *Thomson KR, Cheung W, Ellis SJ et al.* Investigation of the safety of irreversible electroporation in humans. J Vasc Interv Radiol 2011; 22: 611–621
39 *Dritschilo A, Harter KW, Thomas D et al.* Intraoperative radiation therapy of hepatic metastases: technical aspects and report of a pilot study. Int J Radiat Oncol Biol Phys 1988; 14: 1007–1011
40 *Herfarth KK, Debus J, Lohr F et al.* Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. J Clin Oncol 2001; 19: 164–170
41 *Ricke J, Wust P, Stohlmann A et al.* CT-Guided brachytherapy. A novel percutaneous technique for interstitial ablation of liver metastases. Strahlenther Onkol 2004; 180: 274–280
42 *Seidensticker M, Seidensticker R, Mohnike K et al.* Quantitative in vivo assessment of radiation injury of the liver using Gd-EOB-DTPA enhanced MRI: Tolerance dose of small liver volumes. Radiat Oncol 2011; 6: 40
43 *Wallace S, Carrasco CH, Charnsangavej C et al.* Hepatic artery infusion and chemoembolization in the management of liver metastases. Cardiovasc Intervent Radiol 1990; 13: 153–160
44 *Liu DM, Salem R, Bui JT et al.* Angiographic considerations in patients undergoing liver-directed therapy. J Vasc Interv Radiol 2005; 16: 911–935
45 *Denecke T, Ruhl R, Hildebrandt B et al.* Planning transarterial radioembolization of colorectal liver metastases with Yttrium 90 microspheres: evaluation of a sequential diagnostic approach using radiologic and nuclear medicine imaging techniques. Eur Radiol 2008; 18: 892–902
46 *Gray B, Van Hazel G, Hope M et al.* Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol 2001; 12: 1711–1720
47 *Seidensticker R, Seidensticker M, Damm R et al.* Hepatic toxicity after radioembolization of the liver using (90)Y-microspheres: sequential lobar versus whole liver approach. Cardiovasc Intervent Radiol 2011; 35: 1109–1118
48 *Scheele J, Altendorf-Hofmann A, Grube T et al.* Resection of colorectal liver metastases. What prognostic factors determine patient selection? Chirurg 2001; 72: 547–560
49 *Welsh FK, Tekkis PP, O'Rourke T et al.* Quantification of risk of a positive (R1) resection margin following hepatic resection for metastatic colorectal cancer: an aid to clinical decision-making. Surg Oncol 2008; 17: 3–13

Heruntergeladen von: Medizinische Fakultät der Universität Magdeburg. Urheberrechtlich geschützt.

50 *Berber E, Siperstein A.* Local recurrence after laparoscopic radiofrequency ablation of liver tumors: an analysis of 1032 tumors. Ann Surg Oncol 2008; 15: 2757–2764
51 *Mulier S, Ni Y, Jamart J et al.* Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg 2005; 242: 158–171
52 *Van Tilborg AA, Meijerink MR, Sietses C et al.* Long-term results of radiofrequency ablation for unresectable colorectal liver metastases: a potentially curative intervention. Br J Radiol 2011; 84: 556–565
53 *Wu YZ, Li B, Wang T et al.* Radiofrequency ablation vs. hepatic resection for solitary colorectal liver metastasis: A meta-analysis. World J Gastroenterol 2011; 17: 4143–4148
54 *Lambert LA, Colacchio TA, Barth jr. RJ.* Interval hepatic resection of colorectal metastases improves patient selection. Arch Surg 2000; 135: 473–479
55 *Livraghi T, Solbiati L, Meloni F et al.* Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". Cancer 2003; 97: 3027–3035
56 *Kim KH, Yoon YS, Yu CS et al.* Comparative analysis of radiofrequency ablation and surgical resection for colorectal liver metastases. J Korean Surg Soc 2011; 81: 25–34
57 *Aliberti C, Fiorentini G, Muzzio PC et al.* Trans-arterial chemoembolization of metastatic colorectal carcinoma to the liver adopting DC Bead®, drug-eluting bead loaded with irinotecan: results of a phase II clinical study. Anticancer Res 2011; 31: 4581–4587
58 *Stang A, Fischbach R, Teichmann W et al.* A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases. Eur J Cancer 2009; 45: 1748–1756

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Veröffentlichung 3

Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization.

Garlipp B, de Baere T, **Damm R**, Irmscher R, van Buskirk M, Stübs P, Deschamps F, Meyer F, Seidensticker R, Mohnike K, Pech M, Amthauer H, Lippert H, Ricke J, Seidensticker M.

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Left-Liver Hypertrophy After Therapeutic Right-Liver Radioembolization Is Substantial but Less Than After Portal Vein Embolization

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In patients with liver malignancies potentially amenable to curative extended right hepatectomy but insufficient size of the future liver remnant (FLR), portal vein embolization (PVE) of the tumor-bearing liver is used to induce contralateral liver hypertrophy but leaves the tumor untreated. Radioembolization (RE) treats the tumor in the embolized lobe along with contralateral hypertrophy induction. We performed a matched-pair analysis to compare the capacity for hypertrophy induction of these two modalities. Patients with right-hepatic secondary liver malignancies with no or negligible left-hepatic tumor involvement who were treated by right-lobar PVE (n = 141) or RE (n = 35) at two centers were matched for criteria known to influence liver regeneration following PVE: 1) baseline FLR/Total liver volume ratio (<25 versus ≥25%); 2) prior platinum-containing systemic chemotherapy; 3) embolization of segments 5-8 versus 4-8; and 4) baseline platelet count (<200 versus ≥200 Gpt/L).The primary endpoint was relative change in FLR volume from baseline to follow-up. Twenty-six matched pairs were identified. FLR volume increase from baseline to follow-up (median 33 [24-56] days after PVE or 46 [27-79] days after RE) was significant in both groups but PVE produced significantly more FLR hypertrophy than RE (61.5 versus 29%, *P* < 0.001). Time between treatment and follow-up was not correlated with the degree of contralateral hypertrophy achieved in both groups. Although group differences in patient history and treatment setting were present and some bias cannot be excluded, this was minimized by the matched-pair design, as remaining group differences after matching were found to have no significant influence on contralateral hypertrophy development. *Conclusion:* PVE induces significantly more contralateral hypertrophy than RE with therapeutic (nonlobectomy) doses. However, contralateral hypertrophy induced by RE is substantial and RE minimizes the risk of tumor progression in the treated lobe, possibly making it a suitable modality for selected patients. (HEPATOLOGY 2014;59:1864-1873)

Surgical resection remains the only option for cure in patients with primary or secondary malignant liver tumors. Unfortunately, insufficient size of the liver parenchyma that can be preserved (at least 20%-25% in otherwise healthy and 40% in prediseased livers) may preclude surgery.[1] For these cases, preoperative portal vein embolization (PVE) of the tumor-bearing liver lobe has been established over the last 25 years as the standard procedure to induce hypertrophy of the nonembolized liver, resulting in an increase in future liver remnant (FLR) volume of up to 69%.[2] It has been demonstrated that a high degree of post-PVE FLR hypertrophy is associated with a decreased rate of postoperative liver dysfunction[3] and that preoperative PVE has a beneficial effect on postoperative morbidity in patients with chronic liver

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; FLR, future liver remnant; MRI, magnetic resonance imaging; PVE, portal vein embolization; RE, radioembolization; SIRT, selective internal radiation therapy.

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disease undergoing right hepatectomy.[4] However, PVE carries a significant risk of postinterventional tumor progression and may even stimulate tumor growth in the embolized as well as in the nonembolized liver lobe.[5-7] This results in 6.4%-33% of patients becoming unresectable due to tumor progress after PVE.[8,9]

Selective internal radiation therapy (SIRT) or radioembolization (RE) uses the principle of delivering high doses of radiation to liver tumors through infusion of ^{90}Y-labeled glass or resin microspheres into the hepatic arterial circulation of the tumor-bearing liver, thus taking advantage of the preferentially arterial blood supply of the tumor tissue. The technique has been demonstrated to yield high response rates in patients with primary and secondary liver tumors[10,11] and is currently being evaluated for use in the first-line setting in patients with metastatic colorectal cancer in two randomized-controlled trials.[12,13]

Besides the tumoricidal effect, there have been reports on hepatic volume changes induced by unilobar RE, notably significant hypertrophy of the contralateral, nontreated lobe in recent years.[14-19] It has been hypothesized that unilateral RE may achieve a similar extent of contralateral hypertrophy as PVE,[14] in which case it might even be preferable to PVE since it reduces the risk for tumor progression in the treated lobe; however, these modalities have never been directly compared. We therefore analyzed the degree of contralateral liver hypertrophy induction in two cohorts of patients matched for factors known to have an impact on the hepatic hypertrophy response after PVE who underwent either right-lobar PVE or right-lobar RE.

Patients and Methods

Study Design

This retrospective matched pair analysis used pooled data from two centers (center 1: University Hospital Magdeburg, center 2: Institut de cancérologie Gustave Roussy). Patients from center 1 were treated by RE, patients from center 2 by PVE. This study was approved by the local Ethics Committees; the informed consent requirement was waived because of the study's retrospective design. The primary endpoint was the relative increase in volume of the nonembolized liver after RE or PVE (referred to as the FLR in both groups even though RE was performed in a palliative setting and patients receiving RE were not planned to undergo surgery). Secondary endpoints were absolute FLR volume change and absolute as well as relative change in FLR ratio, calculated according to the equation previously published by de Baere et al.[20]:

$$\text{FLR ratio} = \frac{(\text{liver volume}^{\text{FLR}} - \text{tumor volume}^{\text{FLR}})}{(\text{liver volume}^{\text{total}} - \text{tumor volume}^{\text{total}})}$$

Furthermore, toxicities and tumor response after RE were documented.

Patient Characteristics, Eligibility, and Match Criteria

For the RE group from center 1 all patients treated by RE between October 2006 and March 2012 (n = 320) were screened. Inclusion into the analysis was based on the following criteria: 1) no underlying liver cirrhosis; 2) secondary liver malignancy, no primary liver malignancy; 3) magnetic resonance imaging (MRI) of adequate quality before and ~4-6 weeks after RE; 4) disease limited to liver segments IV-VIII or minimal additional disease in liver segments II+III (≤2% tumor load); 5) no liver targeted therapy 3 months prior to RE or between RE and follow-up imaging; 6) availability of liver-specific laboratory parameters and clinical data before and after RE. Thirty-five patients met these criteria. The PVE population comprised 141 patients. The characteristics and clinical outcome of this patient group has been previously published by de Baere et al.[20] Briefly, this patient cohort consisted of noncirrhosis patients with secondary liver malignancies who were deemed to require hypertrophy induction in preparation for extended right hepatectomy due to insufficient volume of the FLR. Out of the identified RE and PVE patients, matched pairs were generated according to the following predefined match criteria: i) baseline FLR ratio

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Additional Supporting Information may be found in the online version of this article.

Table 1. Patient Characteristics

Baseline Characteristics					
	RE		PVE		
Variable	n or mean (median)	SD	n or mean (median)	SD	*P* Value
FLR ratio at baseline (< 25/≥ 25%)	14/12		14/12		1.000
Platelet count at baseline (< 200/≥ 200 Gpt/l)	9/17		9/17		1.000
Prior platinum containing chemotherapy (yes/no)	17/9		17/9		1.000
Segment IV embolized (yes/no)	6/20		6/20		1.000
FLR at baseline (mL)	368.7 (339)	142.2	381.7 (323)	166.0	0.763
FLR ratio at baseline	24.0 (24.4)	7.9	25.5 (24.1)	6.8	0.480
Liver volume embolized at baseline (mL)	1157 (1153)	259.9	1101 (1083)	264.2	0.460
Total liver volume at baseline (mL)	1525 (1447)	308.3	1489 (1446)	373.8	0.712
Ratio embolized to total liver volume at baseline	0.76 (0.76)	0.08	0.74 (0.76)	0.07	0.511
Induction time (days)	46.4 (46)	10.2	34.8 (33)	7.7	<0.001
Platelet count at baseline (Gpt/l)	272.9 (257)	133.5	206.7 (211)	63	0.026
Sex (f/m)	14/2		9/17		0.264
Age (years)	59.2 (58)	11.1	56.1 (56)	7.1	0.235
Age >65y (yes/no)	9/17		3/23		0.097
Weight (kg)	76.7 (79)	13.4	74.5 (73)	14.6	0.601
Height (cm)	168.7 (169)	8.7	171.5 (173)	7.9	0.267
Applied Y90-activity (GBq), RE group only	1.2 (1.2 range: 0.8-1.7)	0.25	n.a.	n.a.	n.a.
Chemotherapy pre treatment (yes/no)	26/0		26/0		1.000
Prior chemotherapy lines (n)					<0.001*
One	6		24		
Two	12		2		
Three	3		0		
Four	4		0		
> four	1		0		
Prior chemotherapy agents (n)					
5-FU/FA	15		23		
Oxaliplatin	10		14		
Cisplatin	4		3		
Carboplatin	3		0		
Irinotecan	9		3		
Capecitabine	3		0		
Bevacizumab	6		0		
Cetuximab	7		0		
Other†					
Primary cancer (mCRC/other)	12/14		22/4		0.008
Primary cancer exact (n)					
CRC	12		22		
Breast	8		2		
Others‡	6		2		

*Comparing "one" vs. "more than one."
†Taxol, epirubicine, anthracyclin, cyclophosphamide, gemcitabine, mytomycin c, vinorelbine, etoposide, trastuzumab.
‡Stomach, anal, laryngeal, urothel, prostate, oropharyngeal, gallbladder.

(<25 versus ≥25%); ii) history of platinum-containing chemotherapy (yes versus no); iii) platelet count (<200 versus ≥200 Gpt/L); iv) degree of embolization (embolization of segments V-VIII versus embolization of segments IV-VIII). Only full matches were accepted. A total of 26 pairs could be matched by these criteria. Patient characteristics of the matched patients are displayed in Table 1.

Technique of ^{90}Y-RE

RE was performed employing Yttrium-90 resin microspheres (SIR-Spheres, Sirtex Medical, Lane Cove, Australia). ^{90}Y is characterized by a mean energy of 0.96 MeV and a half-life of 64 hours. It is coupled to resin microspheres (20 to 60 μm) and infused selectively by way of the hepatic arteries using a transfemoral approach. Treatment including preprocedural diagnostic work-up was performed according to a standard algorithm (detailed description[21]). The activity of ^{90}Y resin microspheres was calculated by the body surface area (BSA) method. For all patients activity was first calculated as for whole-liver treatment and then adjusted for right unilobar treatment according to volume and tumor involvement of the right lobe.[22]

^{90}Y resin microspheres were delivered selectively into the right hepatic artery. All patients received proton pump inhibitors (pantoprazole, 20 mg daily), low-dose prednisolone (5 mg daily), and ursodeoxycholic acid (500 mg daily) for 8 weeks to attenuate the effect of possibly migrated spheres in the gastric mucosa and the embolization effect to the liver parenchyma.[23]

Technique of PVE

The technique of PVE is described by de Baere et al.[20] In brief, access to the portal system was obtained with a left segmental portal branch puncture under sonographic guidance and the right segmental portal veins were selectively catheterized and subsequently embolized one after the other using n-butyl cyanoacrylate suspended in iodized oil. All the branches feeding the tumor-bearing liver were targeted for embolization. Complete occlusion of the targeted portal branches was assessed at the end of the embolization procedure with a direct portography obtained with the tip of the catheter placed in the portal trunk.

No patient underwent any type of chemotherapy in the interval between RE/PVE and post-RE/PVE liver volumetric evaluation.

Image Assessments and Volumetry

RE Group. Routine baseline and follow-up imaging consisted of MRI (1.5T, Achieva, Philips, Best, The Netherlands) using the hepatocyte selective contrast agent Gd-EOB-DTPA (Primovist, Bayer Healthcare, Leverkusen, Germany) prior to (median 16 days before RE, range 1-29 days) and ~6 weeks (median 46 days, range 27-79 days) after RE.

For liver and tumor volumetry (whole liver, FLR, right lobe, tumor for each lobe) a 3D-T1-weighted gradient echo (GRE) sequence (slice thickness 3 mm) obtained 20 minutes after intravenous administration of 0.025 mmol/KG Gd-EOB-DTPA was used. Volumetry and metric measurements were performed with the image processing software Osirix (©Antoine Rosset, 2003-2011).

PVE Group. A computed tomography (CT) scan was performed within a week before PVE and within 3 days before planned liver surgery (median 33 days, range 24-56 days after PVE). After injection of 100 mL iodinated contrast media, maximum 5-mm slices were acquired during the portal phase from the entire liver. The total liver (excluding tumor) and FLR (excluding tumor) were delineated on each image, volumes were calculated automatically by a workstation (Advantage; GE Medical Systems, Milwaukee, WI), taking into account the delineated liver surfaces and slice thickness.

RE-Specific Analyses

Clinical and Toxicity Assessments at Baseline and During Follow-up. All patients had undergone standard clinical and laboratory examinations including liver-related parameters at first presentation and during follow-up after RE. Total serum bilirubin was analyzed before and after embolization. Additionally, the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.02 (National Cancer Institute, USA) were used for toxicity assessments of laboratory values and clinical findings.

Tumor Response After RE. The tumor response after right-liver RE was evaluated using RECIST 1.1 at the time of volumetric measurements (baseline and follow-up 6 weeks after RE). Additionally, the course of disease in the FLR was evaluated according to RECIST 1.1.

Statistical Analyses

Summary statistics of baseline (pretreatment) continuous variables are provided by treatment group and overall as mean ± SD. Frequency distributions of baseline categorical variables are presented by treatment group and overall. *P*-values for treatment comparisons were obtained using a one-way analysis of variance (ANOVA) for continuous variables, Fisher's Exact test for dichotomous categorical variables, and chi-square general association test for nominal categorical variables.

Analysis of the association between baseline covariates and changes (and percent changes) in FLR volume and FLR ratio used an analysis of covariance (ANCOVA) model that includes baseline FLR ratio as the covariate.

Pre- and posttreatment summary statistics are presented with their change (and percent change), along with least-squares (LS) means (and medians) and their standard errors.

Results

Out of the RE and PVE cohorts of 35 and 141 patients, respectively, 26 fully matched pairs according to the predefined criteria could be generated. Thus, the results of all further comparative analyses are based on the matched cohort of 52 patients.

Patient characteristics according to the treatment groups are displayed in Table 1. Significant differences between the groups were seen in the interval between treatment and follow-up imaging (median [range]; RE, 46 [27-79] days; PVE, 33 [24-56] days, $P < 0.001$),

Table 2. Association of Baseline Characteristics and FLR % Change Post-RE or PVE

Variable	*P* Value*	*P* Value†
Match criteria:		
FLR ratio at baseline (< vs. ≥ 25 %)	0.814	
Platelet count at baseline (< vs. ≥ 200 Gpt/l)	0.240	
Prior platinum containing chemotherapy (yes/no)	0.769	
Segment IV embolized (yes/no)	0.300	
Others:		
Treatment (RE vs. PVE)	<0.001	0.022
Sex	0.078	
Age (continuous)	0.623	
Weight (continuous)	0.435	
Height (continuous)	0.023	0.141
primary cancer (mCRC vs. other)	0.036	0.640
Induction time (< vs. ≥ 40 days)	0.036	0.583
Induction time (continuous)	0.473	
Prior chemotherapeutic lines (≤ vs. >1)	0.049	0.560
Prior chemotherapeutic lines (continuous)	0.236	
Platelets at baseline (continuous)	0.075	

*Univariate analysis of categorical (ANCOVA) and continuous (linear regression) baseline variables, association of baseline variables and FLR percent change.

†Multivariate ANCOVA modeling testing independent impact of baseline covariates on FLR percent change.

prevalence of colorectal cancer as the primary cancer site (RE, 12/26 patients; PVE, 22/26 patients, $P = 0.008$), chemotherapy history (more patients with more than one line of prior chemotherapy in the RE group [20/26] compared to the PVE group [2/26]; $P < 0.001$), and platelet count (mean; RE, 272.9 GPt/L, PVE, 206.7 GPt/L, $P = 0.026$). The results of covariate testing of baseline variables (including the match criteria) for possible influence on the primary endpoint variable (relative change in FLR volume after treatment) are displayed in Table 2. With the exception of treatment (RE or PVE), no factor with a significant independent impact was found in the final model. In addition, no significant correlation between the time from treatment to follow-up and the degree of contralateral hypertrophy achieved was found in either group ($P = 0.351$ and $P = 0.135$ for the PVE and RE groups, respectively).

In Table 3 the absolute and relative changes in FLR volume in both groups are summarized. In the RE as well as in the PVE group a significant increase in FLR volume from baseline was noted; however, the relative increase in FLR volume was significantly more pronounced in the PVE group compared to the RE patients (61.5% versus 29%, $P < 0.001$). Similar results were obtained for the FLR ratio, which also significantly increased from baseline in both groups but to a greater extent in the PVE group compared to the RE group (52% versus 30%, $P < 0.001$, data not shown).

When subjects were analyzed according to four categories of relative FLR increase after treatment (≤10%/>10% and ≤20%/>20% and ≤30%/>30%), more patients in the PVE group achieved an FLR increase >30% than in the RE group (PVE; 22 patients, RE; 12 patients). Distribution of patients in the other categories were as follows: ≤10%: 0 versus 5 patients; >10% and ≤20%: 1 versus 6 patients; >20% and ≤30%: 3 versus 3 patients in the PVE and RE group, respectively.

In the full analysis set of all patients irrespective of matching the mean (SD)/median relative FLR changes in the PVE and RE cohorts were 69 (45.5)/57% and 28.4 (20.8)/28.4%, respectively, with a *P*-value for change from baseline within each treatment and between treatments of <0.001 and <0.001, respectively.

In both groups a significant decrease in volume of the embolized liver was noted (RE; −125 mL, $P = 0.002$; PVE; −138 mL, $P < 0.001$) with no significant difference between treatments. The total liver volume showed no significant change after either treatment. The ratio of embolized to total liver volume (at baseline not different between the groups) showed a significant decrease after treatment in both groups. The decrease was significantly more prominent after PVE compared to RE ($P < 0.001$) (Table 4).

Laboratory Values and Toxicities After RE. No significant difference was noted between baseline and follow-up bilirubin levels in the RE patients (baseline, 7.9 [4.1-27.2] μmol/L; follow-up, 8.3 [4.2-20.8] μmol/L; *P* = n.s., upper limit of the norm 21 μmol/L).

Table 3. Group Comparison: Absolute and Relative Change of FLR After Treatment

	RE		PVE		
Variable	Mean (median)	SD	Median (median)	SD	*P* Value
FLR baseline (mL)	368.7 (339)	142.2	381.7 (323)	166.0	0.763
FLR post treatment (mL)	470.6 (435)	203.6	589.5 (535)	221.9	
Change from baseline (mL)	101.9 (80)	106.5	207.9 (176)	114.7	<0.001
Change from baseline (%)	29 (25.3)	22.9	61.5 (50.6)	37.3	<0.001
P value (change from baseline within treatment, both mL and %)	<0.001		<0.001		

Table 4. Changes of Embolized and Total Liver Volume After RE and PVE

Variable	RE		PVE		*P* Value*
	Mean (median)	SD	Mean (median)	SD	
Liver volume embolized at baseline (mL)	1157 (1153)	259.9	1101 (1083)	264.2	0.460*
Liver volume embolized at follow-up after RE/PVE (mL)	1061 (1028)	305	966 (945)	250.8	0.294*
P value (baseline to follow-up)	0.002		<0.001		
Total liver volume at baseline (mL)	1525 (1447)	308.3	1489 (1446)	373.8	0.712*
Total liver volume at follow-up after RE/PVE (mL)	1531 (1558)	354	1566 1432)	391	0.214*
P value (baseline to follow-up)	0.847		0.059		
Ratio embolized to total liver volume at baseline	0.76 (0.76)	0.08	0.74 (0.76)	0.07	0.511*
Ratio embolized to total liver volume at follow-up after RE/PVE	0.69 (0.68)	0.1	0.62 (0.64)	0.09	<0.001*
P value (baseline to follow-up)	<0.001		<0.001		

*RE vs. PVE.

Two grade 3 toxicities were recorded: leukopenia (n = 1) and acute cholecystitis (n = 1). The leukopenia built up on the basis of a preexisting chemotherapy-induced bone marrow toxicity and resolved under treatment with G-CSF. The cholecystitis developed 1 day after RE due to a significant embedding of Y-90 spheres in the cystic artery. After percutaneous drainage of the gall bladder, the situation resolved completely.[24]

Response After Right-Liver RE. According to RECIST 1.1, stable disease in the embolized lobe was seen at follow-up imaging in 19 of 26 RE patients. Partial response was seen in five patients, complete response or progressive disease each occurred in one patient.

Of the 18 patients with preexisting minimal tumor load in the FLR, one patient demonstrated new lesions in the FLR at follow-up. Preexisting lesions in the FLR had increased in size in 10 and remained stable in seven patients at follow-up. One patient without tumor involvement in the FLR at baseline developed tumor lesions in the FLR at follow-up.

Discussion

Along with studies consistently demonstrating high tumor response rates in patients treated with Y-90-labeled microspheres, several reports on volume changes in treated and nontreated areas of the liver have been published in recent years.[14,15,17-19,25] All of these authors reported some degree of increase in volume of the contralateral liver lobe after unilateral RE, leading to a marked interest in further evaluation of a possible therapeutic use of this phenomenon in a surgical context.[14,15] Until now, PVE has been the standard tool to increase FLR volume prior to extensive hepatic resections and therefore we felt that a formal comparison of RE and PVE regarding their respective capacities for hypertrophy induction in the nontreated liver was warranted. To our knowledge, no such study has been published to date.

Development of contralateral hypertrophy following PVE is influenced by several patient- and treatment-related factors, making it impossible to perform a retrospective head-to-head comparison of two patient cohorts treated with either RE or PVE at two different centers. Bearing in mind that a prospective, randomized trial would be optimal in evaluating this issue but would require a large patient cohort and several years to complete, we considered matching patients according to the factors known to influence the degree of hypertrophy following PVE and performed a retrospective analysis, an appropriate method to generate valuable information to allow for the most effective development of future research strategies.

Across publications, it has been consistently demonstrated that the most pronounced liver volume gain after PVE is achieved in patients with the smallest baseline FLR ratio.[20,26,27] This may be due to the fact that the greater the proportion of the liver that is embolized, the more pronounced is the alteration in liver perfusion, leading to a greater extent of cytokine release and redistribution of portal venous blood flow. Second, several authors agree that platinum-containing chemotherapy prior to PVE has a negative impact on regenerative capacity (and thus, hypertrophy induction) in the liver while results with nonplatinum containing chemotherapies as well as targeted therapies have been controversial.[28-33] Platinum-containing chemotherapy is known to induce sinusoidal obstruction syndrome, which may alter portal venous blood flow by itself and thus interfere with the effect induced by subsequent PVE.[20,34,35] Also, embolization of

segment IV together with the right-lobar hepatic segments may influence contralateral volume response, although this could not be reproduced in all trials.[20,36-38] Finally, platelet count has been shown to be predictive of the hepatic regenerative capacity and hypertrophy induction following PVE in experimental and clinical studies, possibly due to its influence on the availability of several platelet-derived growth factors.[39] Taking into account these published data, the criteria for matching patients in the present study were chosen. Other factors known to interfere with regenerative capacity of the liver (e.g., liver cirrhosis, portal hypertension, severe hyperbilirubinemia) were not taken into account since patients with these features were excluded *a priori* from the analysis.

This study demonstrated that, in a cohort of 52 individuals fully matched according to these criteria, unilateral RE resulted in a mean FLR volume increase of 29%, while the mean FLR volume gain induced by PVE was 61.5%. The obvious conclusion from these figures is that PVE remains the standard treatment if maximum FLR volume gain is the goal. However, the hypertrophy-inducing effect of RE should not be disregarded and may be of use in specific patients. The most relevant aspect is that, to date, RE (in contrast to PVE) is primarily used to achieve tumor response, not to induce contralateral hypertrophy. Patients receiving RE are not typically surgical candidates. In our study as well as in most other reports, RE was used as salvage therapy in heavily pretreated patients in a palliative setting using standard therapeutic doses of Y-90, the goal being to treat the tumor without compromising liver function of the normal parenchyma in the treated lobe. With this approach, RE of the contralateral lobe remains an option for a later stage should tumor progression occur there. Thus, induction of hypertrophy was observed as a "side effect" of a treatment that was primarily designed to achieve tumor response and prevent tumor progression in the embolized lobe. This is in line with most published studies evaluating liver volume changes after RE, as standard therapeutic radiation doses were used in almost all of them. Notably, substantial hypertrophy of the nonembolized lobe but no correlation between the applied dose and the extent of hypertrophy obtained were demonstrated in these studies.[14,16,17,19,25] Therefore, we believe that if employed in patients with a small FLR who are potential candidates for surgery, this treatment may open up a curative option for some of these patients and still preserve all further palliative treatment options if cure cannot be achieved. It is likely (and has been demonstrated[18,40]) that with substantially higher cumulative activities of ^{90}Y applied in multiple treatment sessions, the contralateral volume response will be even more pronounced as more periportal fibrosis is induced and portal venous blood is deviated to the contralateral lobe to a greater extent; however, this comes at the cost of ablating functional liver parenchyma ("radiation lobectomy") which may hamper further treatment if contralateral or extrahepatic progression occurs and the setting remains palliative. Moreover, since there is currently no validated method of predicting if and to what extent contralateral hypertrophy will develop after unilateral RE, deliberately applying a dose that will virtually ablate the functional right liver lobe together with the tumor may only be considered if an FLR of sufficient size to compensate for the loss of hepatic function is present from the start,[41] and therefore this approach is not feasible in patients who are considered for hypertrophy induction due to a small-sized FLR since fatal postinterventional liver failure may result. It is important to understand that even the FLR volume gain of roughly 30% observed with RE in our study as well as in other reports,[16] while being clearly inferior to the PVE results, may still convert many patients to resectability. In the full analysis set of RE patients entered into our study ($n = 35$), 9 of the 18 individuals who had a baseline FLR ratio $<25\%$ had an FLR ratio $>25\%$ at follow-up, indicating that volume gain induced by RE may be sufficient to achieve resectability in a substantial proportion of patients. Given the fact that PVE has been demonstrated to increase the tumor growth rate in the treated lobe,[7] RE as a means of hypertrophy induction may be preferable to PVE in patients whose lesions are at risk of becoming unresectable due to invasion of hilar structures or the left hepatic vein if tumor progression occurs, whereas in patients who need maximum FLR volume increase and whose potential plane of resection is not immediately threatened, PVE may remain the treatment of choice (Fig. 1).

There are several limitations to our study which are due to its retrospective nature. The cohorts compared were treated in very different settings. While the majority in the PVE cohort had metastatic colorectal cancer potentially amenable to curative surgery, the RE cohort consisted of heavily pretreated patients with a variety of secondary liver tumors treated with palliative intent. However, there are no data pointing toward an impact of the kind of the liver tumor upon volume response after PVE and publications on the association of prior chemotherapy with liver growth following PVE have yielded varying results. Duration of

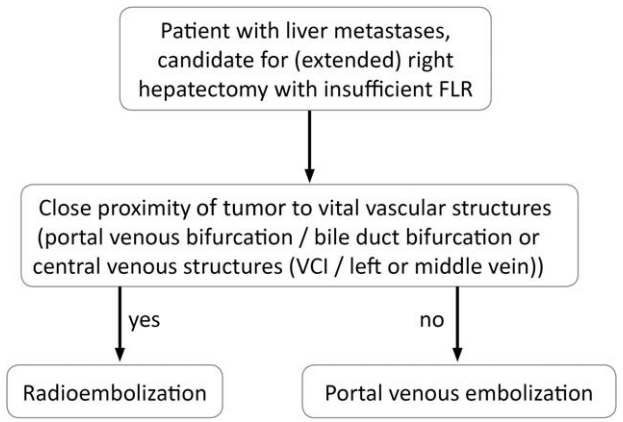

Fig. 1. Suggested treatment pathway for patients requiring FLR hypertrophy induction prior to liver surgery.

previously administered chemotherapy ($\leq$1 versus $>$1 line) had no independent impact as a covariate on hypertrophy induction in our study (Table 2) and patients were matched for history of platinum-containing chemotherapy in accordance with published data, thus minimizing any bias possibly inflicted by different patient history. Because RE is used as a salvage treatment in most centers, an optimal cohort of RE patients to compare with the patients treated with PVE in our study is not available to date. It may also be criticized that the contralateral hypertrophy results obtained in the PVE cohort in our study are in the uppermost range of published figures and other studies have reported substantially less contralateral hypertrophy after PVE.[2] It is likely that this reflects the fact that our PVE patients were treated at a highly specialized center having a very long experience with this treatment and, therefore, the comparison between results obtained with unilateral RE or PVE might have been different if the PVE cohort had been treated at a less experienced institution. However, it is our opinion that a technology that is new in the field should always be tested against the existing standard performed under optimal conditions in order to compare the treatment effect itself and not just different levels of process quality. Because the interest in contralateral hypertrophy induction through RE is relatively new and data on this phenomenon are still sparse and have been obtained in very heterogeneous treatment settings,[14,16,17,19,25] it is difficult to specify how much contralateral hypertrophy can be expected from standard therapeutic-dose unilateral RE; however, reported figures vary between 20.3%[17] and 42%[14] and the mean observed contralateral volume increase in the RE group in our study (29%) falls well within this range, indicating that these results are not biased by any methodological particularity in performing RE at our institution and are likely to be reproduced in other centers. Furthermore, little is known about the kinetics of contralateral volume changes after RE but recent studies suggest that hypertrophy may take substantially longer to develop than after PVE and may even be a continuous process extending beyond 9 months after treatment.[14,19] Therefore, it may be argued that RE may compare more favorably with PVE if more time is allowed between treatment and follow-up imaging. However, hypertrophy induction is relevant in patients who are candidates for surgery and there is a consensus that surgery should be performed as soon as resectability is achieved, because delaying surgery for several months to wait for maximum volume response carries the risk of tumor progression or requires extensive preoperative chemotherapy to eradicate disseminated tumor cells and micrometastases. Hence, for this very first study directly comparing contralateral hypertrophy induction with RE or PVE, an interval of $\sim$6 weeks between RE and follow-up imaging was considered appropriate. Although this was slightly longer than in the PVE cohort, leaving a patient without chemotherapy for 6 weeks is acceptable. Moreover, within the range of intervals used in our matched cohort, the time span between treatment and follow-up was not found to be an independent factor influencing contralateral volume response in the ANCOVA analysis (Table 2) and there was no significant correlation between the time from treatment to follow-up and the degree of contralateral hypertrophy observed in both groups, indicating that the slightly longer waiting time from treatment to follow-up in the RE group did not bias the comparison of contralateral hypertrophy induced by both treatments. Since we were able to demonstrate that RE induces substantial hypertrophy even at a 6-week interval, we feel that a prospective trial comparing PVE and RE a as means of hypertrophy induction is warranted. However, the endpoint of such a trial, which is currently being prepared at our institution, should be resection rate or even survival rather than mere volume increase, because hypertrophy induction is beneficial only if it leads to secondary resectability. Finally, contralateral volume increase after PVE may not always accurately mirror the gain in liver function. It has been demonstrated that FLR function as measured by mebrofenin hepatobiliary scintigraphy may increase to an even greater extent than FLR volume,[42] which may have an impact on clinical outcome.

In conclusion, our study demonstrated that unilateral RE with a standard therapeutic dose produces

significantly less contralateral hypertrophy than PVE within a comparable time frame. However, the hypertrophy induced by RE is substantial and may be sufficient to achieve resectability in many patients, making RE a potentially valuable option for hypertrophy induction in specific situations.

References

1. Azoulay D, Castaing D, Krissat J, Smail A, Hargreaves GM, Lemoine A, et al. Percutaneous portal vein embolization increases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. Ann Surg 2000;232:665-672.
2. Denys A, Prior J, Bize P, Duran R, deBaere T, Halkic N, et al. Portal vein embolization: what do we know? Cardiovasc Intervent Radiol 2012;35:999-1008.
3. Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey J. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. Br J Surg 2007;94:1386-1394.
4. Farges O, Belghiti J, Kianmanesh R, Regimbeau JM, Santoro R, Vilgrain V, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg 2003;237:208-217.
5. Elias D, de Baere T, Roche A, Ducreux M, Leclere J, Lasser P. During liver regeneration following right portal embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma. Br J Surg 1999;86:784-788.
6. Kokudo N, Tada K, Seki M, Ohta H, Azekura K, Ueno M, et al. Proliferative activity of intrahepatic colorectal metastases after preoperative hemihepatic portal vein embolization. Hepatology 2001;34:267-272.
7. Hoekstra LT, van Lienden KP, Doets A, Busch ORC, Gouma DJ, van Gulik TM. Tumor progression after preoperative portal vein embolization. Ann Surg 2012;256:812-817.
8. Di Stefano DR, de Baere T, Denys A, Hakime A, Gorin G, Gillet M, et al. Preoperative percutaneous portal vein embolization: evaluation of adverse events in 188 patients. Radiology 2005;234:625-630.
9. Azoulay D, Castaing D, Smail A, Adam R, Cailliez V, Laurent A, et al. Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. Ann Surg 2000;231:480-486.
10. Sangro B, Iñarrairaegui M, Bilbao JI. Radioembolization for hepatocellular carcinoma. J Hepatol 2012;56:464-473.
11. Wasan H, Kennedy A, Coldwell D, Sangro B, Salem R. Integrating radioembolization with chemotherapy in the treatment paradigm for unresectable colorectal liver metastases. Am J Clin Oncol 2012;35:293-301.
12. Sharma RA, Wasan HS, Love SB, Dutton S, Stokes JC, Smith JL. FOXFIRE: a phase III clinical trial of chemo-radio-embolisation as first-line treatment of liver metastases in patients with colorectal cancer. Clin Oncol (R Coll Radiol) 2008;20:261-263.
13. www.sirflox.com. Accessed Aug 8, 2013.
14. Edeline J, Lenoir L, Boudjema K, Rolland Y, Boulic A, Le Du F, et al. Volumetric changes after (90)Y radioembolization for hepatocellular carcinoma in cirrhosis: an option to portal vein embolization in a preoperative setting? Ann Surg Oncol 2013;20:2518-2525.
15. Fernández-Ros N, Silva N, Bilbao JI, Iñarrairaegui M, Benito A, D'Avola D, et al. Partial liver volume radioembolization induces hypertrophy in the spared hemiliver and no major signs of portal hypertension. HPB (Oxford) 2013 [Epub ahead of print].
16. Ahmadzadehfar H, Meyer C, Ezziddin S, Sabet A, Hoff-Meyer A, Muckle M, et al. Hepatic volume changes induced by radioembolization with (90)Y resin microspheres. A single-centre study. Eur J Nucl Med Mol Imaging 2012;40:80-90.
17. Jakobs TF, Saleem S, Atassi B, Reda E, Lewandowski RJ, Yaghmai V, et al. Fibrosis, portal hypertension, and hepatic volume changes induced by intra-arterial radiotherapy with 90yttrium microspheres. Dig Dis Sci 2008;53:2556-2563.
18. Gulec SA, Pennington K, Hall M, Fong Y. Preoperative Y-90 microsphere selective internal radiation treatment for tumor downsizing and future liver remnant recruitment: a novel approach to improving the safety of major hepatic resections. World J Surg Oncol 2009;7:6.
19. Vouche M, Lewandowski RJ, Atassi R, Memon K, Gates VL, Ryu RK, et al. Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. J Hepatol 2013;59:1029-1036.
20. de Baere T, Teriitehau C, Deschamps F, Catherine L, Rao P, Hakime A, et al. Predictive factors for hypertrophy of the future remnant liver after selective portal vein embolization. Ann Surg Oncol 2010;17:2081-2089.
21. Seidensticker R, Seidensticker M, Damm R, Mohnike K, Schütte K, Malfertheiner P, et al. Hepatic toxicity after radioembolization of the liver using (90)Y-microspheres: sequential lobar versus whole liver approach. Cardiovasc Intervent Radiol 2012;35:1109-1118.
22. Dezarn WA, Cessna JT, DeWerd LA, Feng W, Gates VL, Halama J, et al. Recommendations of the American Association of Physicists in Medicine on dosimetry, imaging, and quality assurance procedures for 90Y microsphere brachytherapy in the treatment of hepatic malignancies. Med Phys 2011;38:4824-4845.
23. Gil-Alzugaray B, Chopitea A, Iñarrairaegui M, Bilbao JI, Rodriguez-Fraile M, Rodriguez J, et al. Prognostic factors and prevention of radioembolization-induced liver disease. Hepatology 2013;57:1078-1087.
24. Kosiek O, Strach K, Pech M, Schulz H, Lippert H, Meyer F. Finding-specific minimally invasive approach for acute radiation-induced cholecystitis after (90)Y-radioembolisation of intrahepatic metastases. Zentralbl Chir 2013:84-87.
25. Gaba RC, Lewandowski RJ, Kulik LM, Riaz A, Ibrahim SM, Mulcahy MF, et al. Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. Ann Surg Oncol 2009;16:1587-1596.
26. Denys A, Lacombe C, Schneider F, Madoff DC, Doenz F, Qanadli SD, et al. Portal vein embolization with N-butyl cyanoacrylate before partial hepatectomy in patients with hepatocellular carcinoma and underlying cirrhosis or advanced fibrosis. J Vasc Interv Radiol 2005;16:1667-1674.
27. Imamura H, Shimada R, Kubota M, Matsuyama Y, Nakayama A, Miyagawa S, et al. Preoperative portal vein embolization: an audit of 84 patients. Hepatology 1999;29:1099-1105.
28. Beal IK, Anthony S, Papadopoulou A, Hutchins R, Fusai G, Begent R, et al. Portal vein embolisation prior to hepatic resection for colorectal liver metastases and the effects of periprocedure chemotherapy. Br J Radiol 2006;79:473-478.
29. Sturesson C, Keussen I, Tranberg K. Prolonged chemotherapy impairs liver regeneration after portal vein occlusion — an audit of 26 patients. Eur J Surg Oncol 2010;36:358-364.
30. Goéré D, Farges O, Leporrier J, Sauvanet A, Vilgrain V, Belghiti J. Chemotherapy does not impair hypertrophy of the left liver after right portal vein obstruction. J Gastrointest Surg 2006;10:365-370.
31. Covey AM, Brown KT, Jarnagin WR, Brody LA, Schwartz L, Tuorto S, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Ann Surg 2008;247:451-455.
32. Zorzi D, Chun YS, Madoff DC, Abdalla EK, Vauthey J. Chemotherapy with bevacizumab does not affect liver regeneration after portal vein embolization in the treatment of colorectal liver metastases. Ann Surg Oncol 2008;15:2765-2772.
33. Simoneau E, Aljiffry M, Salman A, Abualhassan N, Cabrera T, Valenti D, et al. Portal vein embolization stimulates tumour growth in patients with colorectal cancer liver metastases. HPB (Oxford) 2012;14:461-468.
34. Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, et al. Severe hepatic sinusoidal obstruction associated

with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15:460-466.
35. Narita M, Oussoultzoglou E, Chenard M, Rosso E, Casnedi S, Pessaux P, et al. Sinusoidal obstruction syndrome compromises liver regeneration in patients undergoing two-stage hepatectomy with portal vein embolization. Surg Today 2011;41:7-17.
36. Kishi Y, Madoff DC, Abdalla EK, Palavecino M, Ribero D, Chun YS, et al. Is embolization of segment 4 portal veins before extended right hepatectomy justified? Surgery 2008;144:744-751.
37. Nagino M, Kamiya J, Kanai M, Uesaka K, Sano T, Yamamoto H, et al. Right trisegment portal vein embolization for biliary tract carcinoma: technique and clinical utility. Surgery 2000;127:155-160.
38. Massimino KP, Kolbeck KJ, Enestvedt CK, Orloff S, Billingsley KG. Safety and efficacy of preoperative right portal vein embolization in patients at risk for postoperative liver failure following major right hepatectomy. HPB (Oxford) 2012;14:14-19.
39. Nanashima A, Sumida Y, Shibasaki S, Takeshita H, Hidaka S, Sawai T, et al. Parameters associated with changes in liver volume in patients undergoing portal vein embolization. J Surg Res 2006;133:95-101.
40. Iñarrairaegui M, Pardo F, Bilbao JI, Rotellar F, Benito A, D'Avola D, et al. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. Eur J Surg Oncol 2012;38:594-601.
41. Siddiqi NH, Devlin PM. Radiation lobectomy—a minimally invasive treatment model for liver cancer: case report. J Vasc Interv Radiol 2009;20:664-669.
42. de Graaf W, van Lienden KP, van den Esschert JW, Bennink RJ, van Gulik TM. Increase in future remnant liver function after preoperative portal vein embolization. Br J Surg 2011;98:825-834.

Veröffentlichung 4

Safety of repeated radioembolizations in patients with advanced primary and secondary liver tumors and progressive disease after first selective internal radiotherapy.

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Safety of Repeated Radioembolizations in Patients with Advanced Primary and Secondary Liver Tumors and Progressive Disease After First Selective Internal Radiotherapy

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The purpose of this study was to assess the safety of repeated ^{90}Y radioembolization with resin microspheres in patients with extensive primary and secondary liver tumors after failure of first radioembolization. **Methods:** Between 2007 and 2011, 21 patients (12 women, 9 men; mean age, 61.0 y) with nonresectable advanced liver tumors (breast cancer liver metastases, $n = 7$; colorectal liver metastases, $n = 5$; hepatocellular carcinoma, $n = 8$; cholangiocellular carcinoma, $n = 1$) were repeatedly treated by radioembolization. Safety was the primary endpoint. Whole-liver treatment was achieved with sequential treatment sessions in most patients, with selective embolization of the left and right liver lobes within 6 wk. Toxicity was documented prospectively and according to Common Terminology Criteria for Adverse Events 4.0 criteria based on laboratory parameters; magnetic-resonance tomography; and clinical examinations 3 d, 6 wk, and every 3 mo after selective internal radiotherapy (SIRT). Metric variables were evaluated using the Student *t* test. Overall survival was assessed by Kaplan–Meier statistics. **Results:** Patients received an average of 1.6 whole-liver treatments performed in 3.0 unilobar radioembolizations (liver lobes sequentially). The mean total activity administered was 2.57 GBq. No radioembolization-induced liver disease was observed in any of the patients. Three patients showed reversible grade III to IV toxicities according to laboratory values, which returned to pretreatment levels after 6 wk. In 1 patient, a treatment-related duodenal ulcer occurred. Median overall survival was 18 mo after first radioembolization. **Conclusion:** In advanced liver tumors, repeated whole-liver treatments with ^{90}Y radioembolization can be performed with an acceptable toxicity profile.

Key Words: liver malignancies; repeated radioembolization; ^{90}Y microspheres; sequential approach; toxicity

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The liver is a common site of metastasis in various tumors, for example, colorectal cancer or breast cancer (*1,2*). Unfortunately, most patients with liver metastasis will face advanced-stage disease, lacking curative options. Furthermore, malignancies with the liver as the primary site, such as hepatocellular carcinoma (HCC) or cholangiocellular carcinomas, are—despite advances throughout surveillance programs in risk groups—not likely to be diagnosed until there is extended disease (*3,4*). In this palliative situation, and given the incidence of extrahepatic tumor spread, effective treatment and control of the hepatic tumor load may be, especially in colorectal liver metastases, of the utmost importance for survival (*5*). Radioembolization using ^{90}Y microspheres is a relatively new modality applicable even in patients with extensive primary and secondary liver neoplasms. Recent experience indicates the efficacy of radioembolizations in these patients (*6–11*), but there is still a lack of evidence from randomized controlled trials such as have been published on systemic chemotherapies (especially colorectal liver metastases) or transarterial chemoembolization (HCC) (*12,13*).

Radioembolization is, therefore, frequently placed at the end of therapeutic management, and as of today radioembolization is conducted predominantly after failure of conventional therapies. In that regard, radioembolization is seen as an exceptional salvage treatment usually conducted at just 1 time point per patient. The absence of alternative treatment options after an initial radioembolization raises the question of whether repeated radioembolization would be safe and effective. In individual patients, the indication for repeated radioembolizations may vary, with indication for repeated whole-liver or lobar radioembolization. Safety is of considerable interest in patients with restricted liver function after previous radioembolization, possibly in combination with hepatotoxic chemotherapies or liver cirrhosis.

In this study, we retrospectively reviewed 21 patients who had undergone repeated radioembolizations of one or both liver lobes. The primary endpoint was safety of the repeated radioembolization, with specific emphasis on liver function during follow-up. Survival analysis was also performed.

MATERIALS AND METHODS

Patients

Between 2007 and 2011, 21 patients (12 women, 9 men; mean age, 61.0 y [range, 34–75 y]) with nonresectable advanced liver tumors (breast cancer, $n = 7$; colorectal cancer, $n = 5$; HCC, $n = 8$; cholangiocellular carcinoma, $n = 1$) were repeatedly treated by radioembolization (at least 3 lobar procedures).

The indications for the initial radioembolization were disease relapse after various pretreatments, including liver resection in most patients. Prior treatments included surgical procedures in 6 patients and local ablations in 4 patients. Fifteen patients had previously been treated systemically with an average of 2 lines of chemotherapy.

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Furthermore, we recorded all concomitant treatments for method (e.g., radiofrequency ablation) and location. Details of patient characteristics are shown in Table 1.

Patients presenting with liver cirrhosis and Child–Pugh category C were not offered radioembolization. Among the patients with HCC, 6 presented with Child–Pugh stage A (5–6 points) and 2 with stage B (7 points). Inclusion criteria for all patients at initial or repeated radioembolizations comprised an East Coast Oncology Group (ECOG) performance status of 0–2, a Karnofsky index above 70%, a platelet count above 50,000, a prothrombin time of at least 50%, and bilirubin below 30 μmol/L. Controlled ascites and partial portal-vein occlusion were not exclusion criteria.

Extrahepatic metastases were found in 9 of 18 patients at the time of intervention. In these patients, a dominant hepatic tumor load to the liver was considered the most relevant prognostic factor for survival and therefore patients were offered radioembolizations if systemic options were not available or were refused by the patient. The decision for a repetitive radioembolization cycle was based on the response after the initial radioembolization. As a consequence, patients with early progression, observed 6 wk after the first radioembolization, were excluded from repeated treatment. Sixteen patients received 3 lobar radioembolizations, 4 patients were treated with 4, and 1 patient was treated with 5. Patients were exclusively treated 1 lobe at a time. If for a single radioembolization cycle both liver lobes were scheduled for radioembolization, the interval between radioembolizations of both lobes was 4–6 wk.

Expressed as a cumulative exposure, patients received 1.6 whole-liver treatments applied on average in 3 unilobar sessions.

Measurements of tumor and uninvolved liver parenchyma were performed on the basis of pretherapeutic MR imaging scans with a hepatocyte-specific contrast agent. The median pretherapeutic volume of uninvolved liver parenchyma was 1,580 mL (range, 1,032–2,410 mL), and the median tumor volume was 201 mL (100–695 mL). The tumor volume as a fraction of the total liver volume (median, 1,755 mL [1,287–2,972 mL]) ranged between 4% and 29% (median, 12%).

All patients underwent the standard evaluation procedure at our institution including a physical examination, liver function tests, and extensive tumor staging.

TABLE 1
Patient Characteristics

Characteristic	Data (n = 21)
Sex	
Male	9
Female	12
Cancer type	
Colorectal cancer	5
Breast cancer	7
HCC	8
Cholangiocellular carcinoma	1
Age (y)	
Mean	61
Range	34–75
Initial tumor load (%)	
Mean	19
Range	5–50
Extrahepatic metastases present	11
Concomitant treatment	
Local ablation	4
Sorafenib	4 (of 8 HCC patients)
Systemic chemotherapy	2

The local ethics committee approved this retrospective study, and the requirement to obtain an informed consent was waived.

Radioembolization Technique

Radioembolization comprises the injection of radioactive ^{90}Y-labeled resin microspheres (SIR-Spheres; Sirtex Medical) into the arterial hepatic circulation. Resin microspheres accumulate specifically in tumor tissue because tumors almost exclusively receive their blood supply from the hepatic artery. Antitumor efficacy is linked to the β radiation from ^{90}Y, which decays with a physical half-life of 64 h (~2.7 d).

Before radioembolization, angiography of the celiac trunk was performed; this usually included coil embolization of the gastroduodenal artery, right gastric artery, and cystic artery to avoid extrahepatic accumulation of microspheres in the therapy session. After coil embolization, ^{99m}Tc-MAA (^{99m}Tc bound to macroaggregated albumin) was injected into the right and left hepatic artery to rule out a relevant shunt volume to the lung and extrahepatic accumulation (e.g., in the stomach). A shunt fraction exceeding 20% of the total was considered a contraindication for radioembolization, whereas 10%–20% resulted in a dose reduction as recommended in the specification of product characteristics for the microspheres. With a typical delay of 2–3 wk after the diagnostic scan, therapy (treatment cycle) with ^{90}Y-labeled resin microspheres was conducted in 2 separate sessions (procedures) with selective injection of ^{90}Y-labeled microspheres into the right and left hepatic artery and separated by an interval of 4–6 wk. The intrahepatic distribution of ^{90}Y-labeled resin microspheres was assessed using Bremsstrahlung and SPECT imaging, and the distribution of ^{99m}Tc-MAA was assessed using SPECT imaging.

Before initiation of another therapy cycle after progression, angiography and ^{99m}Tc-MAA scintigraphy were repeated to exclude extrahepatic accumulations caused by collaterals or by shunts to the lung that have increased in the meantime.

Activity Calculation

The body surface area (BSA) method was used to calculate the required dose (*14,15*).

Following the recommendations of Kennedy et al., BSA was calculated as follows:

$\text{BSA } (m^2) = 0.20247 \times \text{height } (m)^{0.725} \times \text{weight } (kg)^{0.425}$. The activity administered was calculated as follows: activity (GBq) = (BSA − 0.2) + tumor volume/total liver volume.

The prescribed dose was not reduced because of a repeated radioembolization; it was, however, reduced in cases of an increased shunt volume. Activity calculation for the first and second radioembolizations followed the same algorithm.

As mentioned above, the dose was administered sequentially to each liver lobe separately, with an interval of 4–6 wk between the sessions.

Endpoints, Assessments, and Statistical Methods

Primary endpoints were toxicities (acute and subacute), and the secondary endpoint was overall survival (OS). Before therapy, a physical examination; MR and CT imaging; and laboratory tests including total bilirubin, alanine transaminase, aspartate transaminase, alkaline phosphatase, γ glutamyl transpeptidase, and albumin were performed. All these were repeated 6 wk and 3 mo after radioembolization and thereafter every 3 mo.

MR imaging scans were obtained in a 1.5-T system, before radioembolization and 6 wk and 3 mo after the completion of therapy and then every 3 mo thereafter to monitor tumor response and time to progression (TTP). The hepatocyte-specific contrast agent Gd-EOB-DTPA (Primovist; Bayer) was used. Common side effects of radioembolization (e.g., ascites, pleural effusion) were graded in conjunction with imaging findings. Furthermore, patients were examined for clinical signs of radioembolization-induced liver disease (REILD) according to Sangro et al. (*16*).

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Toxicities were graded by the Common Terminology Criteria for Adverse Events (CTCAE), version 4.02, on the basis of laboratory values, MR imaging, and clinical examinations. Grading was performed 3 d and 6 wk after SIRT and then every 3 mo.

TTP was assessed according to the modified Response Evaluation Criteria In Solid Tumors (*17*) and defined as the time from the first procedure to the first assessment showing intrahepatic progression. OS was defined as the time from the first procedure to the patient's death.

The program suite PASW Statistics 18.0.0 (Polar Engineering and Consulting) was used for statistical analysis. Metric variables were calculated by the Student *t* test and nonmetric by the Wilcoxon test. Frequencies were assessed by the Fisher exact test. Survival was estimated by the Kaplan–Meier method. *P* values below 0.05 were considered to be significant at the descriptive level of this study.

RESULTS

The mean total whole-liver activity administered (cumulative activity applied; the cumulative sum of the activities administered in all single sessions) was 2.57 GBq (range, 1.55–4.15 GBq; SD, 0.63 GBq).

Before the first treatment, the mean pulmonary shunt of all patients was 5.4% (2.0%–14.4%; SD, 3.0). Reevaluation before the second treatment cycle did not show a significant increase in the shunt volume. Nevertheless, the calculated dose had to be reduced in 5 patients because of the increasing shunt volume. The mean dose administered to the same lobe decreased from 0.97 GBq in the first session to 0.88 GBq in the second session ($P > 0.05$).

Between radioembolization cycles, 4 patients were treated with local ablation for small focal lesions. Four patients with HCC were treated with sorafenib (Nexavar; Bayer). Two patients with liver metastases received a systemic treatment during the observation period. Table 2 provides a summary of treatment characteristics.

Safety and Complications

No REILD was observed in any of the patients. In patients with liver cirrhosis ($n = 8$), no significant worsening of the Child–Pugh class was observed. Two patients showed an increase (5–6 points and 6–7 points, respectively) and another 2 patients a decrease in Child–Pugh score by 1 point. Between patients with and without cirrhosis, no statistically significant differences were seen with respect to liver function toxicities at any time point.

Furthermore, when bilirubin level was investigated as a surrogate of liver function, no significant correlation was found between cumulative activity and the increase of bilirubin level during the observation.

Total numbers of adverse events in treatment cycle 1 were 22 events for patients with HCC ($n = 8$) and 35 for all other patients ($n = 13$). Total numbers of adverse events in treatment cycle 2 were 27 events for patients with HCC ($n = 8$) and 44 for all other patients ($n = 13$). No grade IV or grade V events were recorded after initial or repeated radioembolization procedures. In treatment cycle 1, adverse events of CTCAE grade I, II, and III were reported for 75%, 50%, and 13% (respectively) of the patients with HCC and for 92%, 38%, and 8% of all other patients. In treatment cycle 2, the respective numbers of patients were 100%, 25%, and 0% for the patients with HCC and 92%, 54%, and 8% of all other patients (Table 3).

Most frequent adverse events were ascites, elevation of bilirubin or liver enzymes, and decrease of serum albumin levels (Table 4). Grade II laboratory events were seen in 8 cases, of which 4 had resolved by the time of the next radioembolization procedure. Three patients showed reversible grade III toxicities in laboratory values that returned

TABLE 2
Previous Systemic Treatments

Patient no.	Diagnosis	No. of lines	Schemes and substances
1	Colorectal cancer	1	FOLFOX/cetuximab
2	Breast cancer	5	FEC, vinorelbine/trastuzumab, capecitabine/trastuzumab, paclitaxel/trastuzumab, capecitabine/lapatinib
3	Colorectal cancer	1	FOLFIRI/bevacizumab
4	HCC	0	
5	HCC	0	
6	Cholangiocellular carcinoma	4	FUFOX, gemcitabine, sorafenib, cetuximab
7	Colorectal cancer	3	FOLFOX, FOLFIRI, FOLFIRI/bevacizumab
8	HCC	1	Sorafenib
9	Breast cancer	5	Paclitaxel/epirubicin, docetaxel/capecitabine, docetaxel/5-fluorouracil, vinorelbine, doxorubicin
10	Colorectal cancer	0	
11	HCC	0	
12	Breast cancer	1	Docetaxel
13	HCC	1	Sorafenib
14	HCC	1	Sorafenib
15	Colorectal cancer	1	FOLFIRI
16	Breast cancer	1	Capecitabine
17	Breast cancer	2	FEC, aromatasin inhibitor
18	Breast cancer	4	FEC, docetaxel, capecitabine, doxorubicin
19	Breast cancer	2	FEC, vinorelbine/capecitabine
20	HCC	1	Sorafenib
21	HCC	1	Sorafenib

FOLFOX = folinic acid, fluorouracil, oxaliplatin; FEC = fluorouracil, epirubicin, cyclophosphamide; FOLFIRI = folinic acid, fluorouracil, irinotecan; FUFOX = fluorouracil, folinic acid, oxaliplatin.

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TABLE 3
Frequency of Adverse Events

Parameter	Cycle	Grade I	Grade II	Grade III
No. of CTCAEs				
HCC (n = 8)	1	16	5	1
	2	25	2	0
Metastases/cholangiocellular carcinoma (n = 13)	1	28	6	1
	2	31	12	1
Percentage of patients (%)				
HCC (n = 8)	1	75	50	13
	2	100	25	—
Metastases/cholangiocellular carcinoma (n = 13)	1	92	38	8
	2	92	54	8

to pretreatment levels after 6 wk (Tables 4 and 5). In 1 patient, a treatment-related duodenal ulcer (grade II) occurred after 3 mo.

A significant increase in mean total bilirubin level (up to 1.6 times the pretreatment level) was seen during the observation period. However, despite that increase, all bilirubin values remained within normal limits (Fig. 1).

Four patients developed ascites or increase of bilirubin that was due to intrahepatic tumor progression within the 3 mo after the last radioembolization. No radiation-induced pneumonitis was observed.

TTP and OS

The median duration of follow-up (including MR imaging to assess TTP) was 10 mo (range, 5–38 mo). The median TTP after the first radioembolization was 3.0 mo after the start of the first treatment session. At the time of this analysis, 13 patients had died; the median OS was 18 mo (Fig. 2).

DISCUSSION

In patients with advanced primary or secondary liver neoplasms confined to the liver with or without minor extrahepatic spread of the disease, there is debate as to what constitutes optimum therapeutic management. Whereas a lack of alternatives after failure of an established chemotherapy regimen eases the decision for radioembolization of the liver, the question of to where radioembolization needs to be placed in the therapeutic algorithm is still open and simple answers are unlikely to be forthcoming in the near future because of the lack of randomized controlled trials. In HCC, results from recent single-arm phase II trials have led the debate in the direction of the competition with transarterial chemoembolization (TACE). However, currently available data suggest that radioembolization is best placed after the failure of TACE in early intermediate-stage HCC (European Association for the Study of the Liver/European Organisation for Research and Treatment of Cancer guidelines) or in patients with diffuse disease (>4 tumors) or large tumors (>5 cm) (*18*). The clearest difference between radioembolization and TACE is, however, the fact that TACE has evolved as a repetitive procedure, which is not the case for radioembolization (*13*). Despite the fact that its effect vanishes over time, radioembolization has been adopted as a single-application therapeutic approach. In HCC, the only current prospective randomized study considering repetitive treatments in intermediate- and advanced-stage HCC is SORAMIC (*19*), which is expected to continue recruitment until 2014.

Besides HCC, the next most common indications for radioembolization are colorectal cancer, breast cancer, and others including neuroendocrine liver metastases. In all these tumors, radioembolization has demonstrated high tumor response rates in phase II studies, but despite the fact that a reasonable response rate could probably be expected by second or third radioembolization procedures, data on such an approach are scarce.

TABLE 4
Treatment Characteristics

Characteristic	Data	Statistical significance
No. of radioembolization procedures (unilobar)		
3	16	
4	4	
5	1	
Mean no. of whole-liver radioembolization per patient	1.6	
Shunt (%)		
First evaluation	5.4 (n = 21)	
Second evaluation	9.8 (n = 14)	$P > 0.05$
Dose reduction	5	
Cumulative total dose applied (GBq)		
Mean	2.57	
SD	0.63	
Range	1.55–4.15	

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TABLE 5
Severity and Type of Adverse Events

CTCAE toxicity	Grade	Liver metastases (n = 13)	HCC (n = 8)
Ascites	I	6 (46)	3 (38)
	II		1 (13)
Pleural effusion	I	2 (15)	
Bilirubin	I	4 (30)	
	II	3 (23)	2 (25)
Albumin	I	5 (39)	5 (63)
	II		2 (25)
Liver enzymes*	I	6 (46)	6 (75)
	II	5 (39)	1 (13)
	III	2 (15)	1 (13)
Duodenal ulcer	II	1 (8)	

*Glutamate pyruvate transaminase/glutamic oxaloacetic transaminase/alkaline phosphatases.
Data in parentheses are percentages.

The reason for the lack of data on repetitive radioembolization is probably that the risk of toxic liver function deterioration—such as through REILD—is significant, specifically in salvage patients. In a study by Sangro et al., 30% of patients with liver metastases developed clinical symptoms of REILD after total liver irradiation (*16*). Risk factors were young age, previous chemotherapies containing 5-fluorouracil, and low tumor volume in small livers. A recent publication by the group of Seidensticker et al. (*20*) describes a significant risk reduction for liver function deterioration or REILD. In that study, patients received either total liver radioembolization in a single treatment or sequential lobar treatments at intervals of 4–6 wk. In the latter group, bilirubin increase and portal hypertension including ascites were displayed significantly less frequently.

The present study is the first report, to our knowledge, on repetitive liver treatment by radioembolization in cases with disease progression after the first intervention in a larger patient cohort. In our patient group, treated exclusively with a sequential lobar approach, repeated radioembolization had a high safety profile. No REILD was observed. No significant differences in toxicity profile between patients with and without cirrhosis were evident. In no patient was a significant worsening of liver function noted.

Radioembolization was performed repeatedly in one or both liver lobes with predominantly minor toxicities, maintaining the ECOG performance stage and the liver function with respect to the Child–Pugh score. Overall, up to 5 procedures could safely be performed in individual patients. The frequency and severity of toxicity were not different from, or even lower than, those reported in other radioembolization trials (*21–24*). The reason for that is indubitably a strong patient selection in terms of liver function, especially bilirubin level, and the sequential approach chosen (*20*). At our institution, a bilirubin level exceeding 30 μmol/L disqualifies a patient for radioembolization.

Despite a significant increase in the mean total bilirubin level during follow-up, bilirubin values always remained within reference ranges during the observation period.

Recently, Lam et al. (*25*) reported an interesting case series of 8 patients undergoing repeated radioembolization out of 247 patients treated with radioembolization. The cumulative dose of these 8 patients ranged between 2.41 and 3.88 GBq. Two patients developed symptoms of REILD. Both had received whole-liver treatments with a cumulative dose of 3.08 and 2.66 GBq, and at least one radioembolization was performed in a single-session whole-liver treatment approach, with the resin microspheres administered into the proper or common hepatic artery. This was not the case in our patient cohort, in which a strictly sequential approach in a lobar manner with an interval of 4–6 wk between the sessions was performed.

Both our study and that of Lem et al. failed to detect a significant correlation between activity administered and development of REILD.

Despite the fact that Lem et al. did not find the treatment approach to be a statistically significant factor for REILD, nevertheless

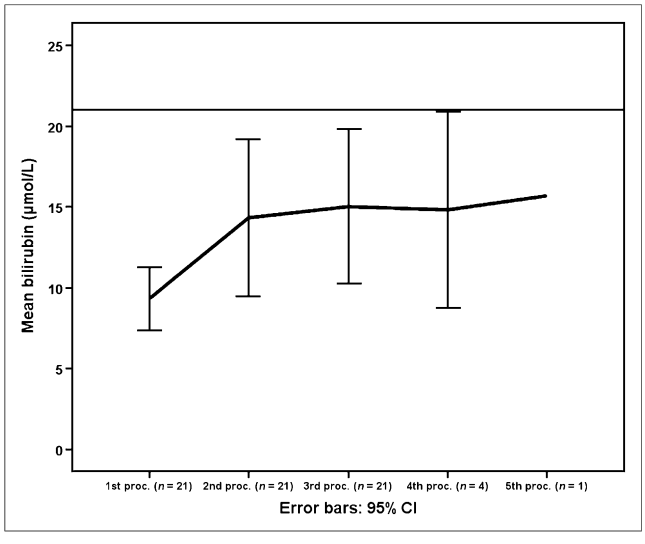

FIGURE 1. Bilirubin trend during observation period. CI = confidence interval; proc. = procedure.

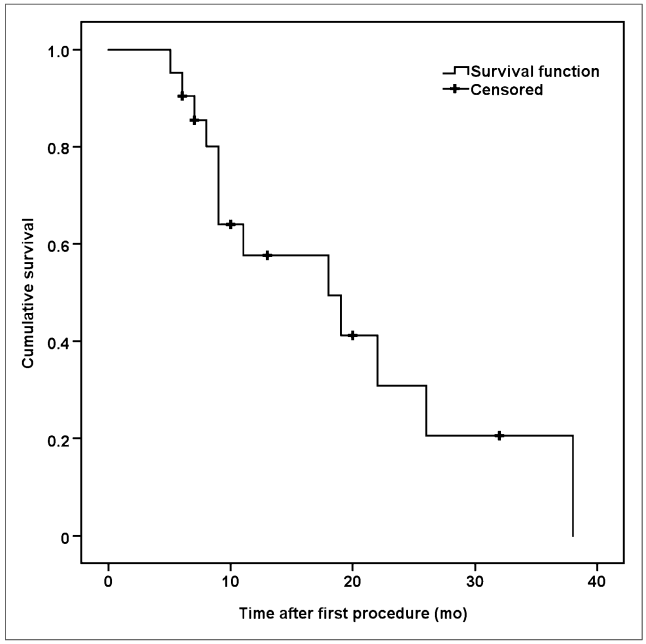

FIGURE 2. OS (mo).

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9 of 10 patients in their trial developed REILD after a whole-liver treatment (162 patients, 5.5% REILD), compared with 1 after lobar–segmental radioembolization (75 patients, 1.3% REILD). Therefore, the risk of developing REILD was more than 4 times greater in patients receiving single-session whole-liver treatments.

In addition, and as mentioned earlier in this section, the work of Seidensticker et al. revealed a significant difference in terms of toxicities, with significantly better tolerance to radioembolization in the patient group with sequential lobar treatments than in patients receiving single-session whole-liver treatments (*20*). These results are supported by the data of Ricke, Ruehl, and Seidensticker (*26–28*), whose research findings in MR imaging examinations with a hepatocyte-specific contrast agent (Primovist; Bayer) documented repair mechanisms over time after high-dose-rate brachytherapy of liver metastases after a transient hepatocyte function loss following exposure to a specific radiation dose.

All of our patients received the sequential approach. Therefore, and besides other safety constraints (see above), the probability of the development of REILD induction was lower in our patient cohort.

OS was promising, with a median of 18 mo, when compared with published outcomes after radioembolization or second- to third-line chemotherapy.

For colorectal liver metastases, an OS of 14.5 mo (*29*), 10.5 mo (*30*), and 10 mo (*31*) have been reported. Seidensticker et al. showed the superiority of radioembolization over best supportive care for colorectal liver metastases (*32*).

Salem et al. reported an OS of 17.2 and 7.7 mo for 291 patients with HCC, depending on the Child–Pugh stage (A or B) (*33*).

There is broad evidence for the efficacy of second- to third-line chemotherapy. In a second-line situation, a FOLFIRI regimen in 213 patients resulted in a progression-free survival of 5.1 mo (*34*). In a third-line situation, bevacizumab plus FOLFIRI (folinic acid, fluorouracil, irinotecan) or FOLFOX (folinic acid, fluorouracil, oxaliplatin) resulted in a progression-free survival and OS of 5.3 and 9.5 mo, respectively (*35*). Adverse events in the aforementioned trial included grade III to IV neutropenia in approximately 43%, fatigue in 22%, neuropathy in 22%, and mucositis in 22% of all patients.

Taking into account the heterogeneity with 12 secondary liver neoplasms and 9 primary liver tumors in our study, the OS of 18 mo in our patient cohort indicates a possible benefit also in terms of effectiveness. Nevertheless, this is a safety study, and prospective trials with a larger cohort are needed to prove a benefit with respect to OS after repeated radioembolizations.

CONCLUSION

Repetitive radioembolization was demonstrated to be safe in our patients with preserved liver function. Our results encourage one to consider radioembolization in patients with tumor recurrences after failed initial radioembolization and without alternative treatment options. Future studies should evaluate the effectiveness of repeated radioembolizations, specifically with regard to response rates as compared with the initial radioembolization.

DISCLOSURE

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REFERENCES

1. Simmonds PC, Primrose JN, Colquitt JL, et al. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer.* 2006;94:982–999.
2. Mayo SC, Pawlik TM. Current management of colorectal hepatic metastasis. *Expert Rev Gastroenterol Hepatol.* 2009;3:131–144.
3. Lencioni R, Chen XP, Dagher L, et al. Treatment of intermediate/advanced hepatocellular carcinoma in the clinic: how can outcomes be improved? *Oncologist.* 2010;15(suppl 4):42–52.
4. Yachimski P, Pratt DS. Cholangiocarcinoma: natural history, treatment, and strategies for surveillance in high-risk patients. *J Clin Gastroenterol.* 2008;42:178–190.
5. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. *BMJ.* 2000;321:531–535.
6. Kennedy AS, McNeillie P, Dezarn WA, et al. Treatment parameters and outcome in 680 treatments of internal radiation with resin ^{90}Y-microspheres for unresectable hepatic tumors. *Int J Radiat Oncol Biol Phys.* 2009;74:1494–1500.
7. Rowe BP, Weiner R, Foster J, et al. ^{90}Yttrium microspheres for nonresectable liver cancer: the University of Connecticut Health Center experience. *Conn Med.* 2007;71:523–528.
8. Lin M, Shon IH, Wilson R, et al. Treatment response in liver metastases following ^{90}Y SIR-spheres: an evaluation with PET. *Hepatogastroenterology.* 2007;54:910–912.
9. Garrean S, Muhs A, Bui JT, et al. Complete eradication of hepatic metastasis from colorectal cancer by yttrium-90 SIRT. *World J Gastroenterol.* 2007;13:3016–3019.
10. Szyszko T, Al-Nahhas A, Canelo R, et al. Assessment of response to treatment of unresectable liver tumours with ^{90}Y microspheres: value of FDG PET versus computed tomography. *Nucl Med Commun.* 2007;28:15–20.
11. Welsh JS, Kennedy AS, Thomadsen B. Selective internal radiation therapy (SIRT) for liver metastases secondary to colorectal adenocarcinoma. *Int J Radiat Oncol Biol Phys.* 2006;66:S62–S73.
12. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359:378–390.
13. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet.* 2002;359:1734–1739.
14. Dezarn WA, Cessna JT, DeWerd LA, et al. Recommendations of the American Association of Physicists in Medicine on dosimetry, imaging, and quality assurance procedures for ^{90}Y microsphere brachytherapy in the treatment of hepatic malignancies. *Med Phys.* 2011;38:4824–4845.
15. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. *Int J Radiat Oncol Biol Phys.* 2007;68:13–23.
16. Sangro B, Gil-Alzugaray B, Rodriguez J, et al. Liver disease induced by radioembolization of liver tumors: description and possible risk factors. *Cancer.* 2008;112:1538–1546.
17. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205–216.
18. Hu HT, Kim JH, Lee LS, et al. Chemoembolization for hepatocellular carcinoma: multivariate analysis of predicting factors for tumor response and survival in a 362-patient cohort. *J Vasc Interv Radiol.* 2011;22:917–923.
19. *Clin Trials.* www.clincialtrials.gov. NCT01126645. 2013.
20. Seidensticker R, Seidensticker M, Damm R, et al. Hepatic toxicity after radioembolization of the liver using ^{90}Y-microspheres: sequential lobar versus whole liver approach. *Cardiovasc Intervent Radiol.* 2012;35:1109–1118.

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21. Goin JE, Salem R, Carr BI, et al. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: factors associated with liver toxicities. *J Vasc Interv Radiol.* 2005;16:205–213.
22. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology.* 2011;140:497–507.
23. Mancini R, Carpanese L, Sciuto R, et al. A multicentric phase II clinical trial on intra-arterial hepatic radiotherapy with 90yttrium SIR-spheres in unresectable, colorectal liver metastases refractory to i.v. chemotherapy: preliminary results on toxicity and response rates. *In Vivo.* 2006;20:711–714.
24. Rühl R, Seidensticker M, Peters N, et al. Hepatocellular carcinoma and liver cirrhosis: assessment of the liver function after yttrium-90 radioembolization with resin microspheres or after CT-guided high-dose-rate brachytherapy. *Dig Dis.* 2009;27:189–199.
25. Lam MG, Louie JD, Iagaru AH, et al. Safety of repeated yttrium-90 radioembolization. *Cardiovasc Intervent Radiol.* 2013;36:1320–1328.
26. Seidensticker M, Seidensticker R, Mohnike K, et al. Quantitative in vivo assessment of radiation injury of the liver using Gd-EOB-DTPA enhanced MRI: tolerance dose of small liver volumes. *Radiat Oncol.* 2011;6:40.
27. Rühl R, Ludemann L, Czarnecka A, et al. Radiobiological restrictions and tolerance doses of repeated single-fraction hdr-irradiation of intersecting small liver volumes for recurrent hepatic metastases. *Radiat Oncol.* 2010;5:44.
28. Ricke J, Seidensticker M, Ludemann L, et al. In vivo assessment of the tolerance dose of small liver volumes after single-fraction HDR irradiation. *Int J Radiat Oncol Biol Phys.* 2005;62:776–784.
29. Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. *Cancer.* 2009;115:1849–1858.
30. Jakobs TF, Hoffmann RT, Dehm K, et al. Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. *J Vasc Interv Radiol.* 2008;19:1187–1195.
31. Sato KT, Lewandowski RJ, Mulcahy MF, et al. Unresectable chemorefractory liver metastases: radioembolization with ^{90}Y microspheres—safety, efficacy, and survival. *Radiology.* 2008;247:507–515.
32. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol.* 2012;35:1066–1073.
33. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology.* 2010;138:52–64.
34. Muro K, Boku N, Shimada Y, et al. Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study). *Lancet Oncol.* 2010;11:853–860.
35. Kang BW, Kim TW, Lee JL, et al. Bevacizumab plus FOLFIRI or FOLFOX as third-line or later treatment in patients with metastatic colorectal cancer after failure of 5-fluorouracil, irinotecan, and oxaliplatin: a retrospective analysis. *Med Oncol.* 2009;26:32–37.

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Safety of Repeated Radioembolizations in Patients with Advanced Primary and Secondary Liver Tumors and Progressive Disease After First Selective Internal Radiotherapy

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Veröffentlichung 5

Prospective randomized trial of enoxaparin, pentoxifylline and ursodeoxycholic acid for prevention of radiation-induced liver toxicity.

Seidensticker M, Seidensticker R, **Damm R**, Mohnike K, Pech M, Sangro B, Hass P, Wust P, Kropf S, Gademann G, Ricke J.

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Prospective Randomized Trial of Enoxaparin, Pentoxifylline and Ursodeoxycholic Acid for Prevention of Radiation-Induced Liver Toxicity

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Abstract

Background/Aim: Targeted radiotherapy of liver malignancies has found to be effective in selected patients. A key limiting factor of these therapies is the relatively low tolerance of the liver parenchyma to radiation. We sought to assess the preventive effects of a combined regimen of pentoxifylline (PTX), ursodeoxycholic acid (UDCA) and low-dose low molecular weight heparin (LMWH) on focal radiation-induced liver injury (fRILI).

Methods and Materials: Patients with liver metastases from colorectal carcinoma who were scheduled for local ablation by radiotherapy (image-guided high-dose-rate interstitial brachytherapy) were prospectively randomized to receive PTX, UDCA and LMWH for 8 weeks (treatment) or no medication (control). Focal RILI at follow-up was assessed using functional hepatobiliary magnetic resonance imaging (MRI). A minimal threshold dose, i.e. the dose to which the outer rim of the fRILI was formerly exposed to, was quantified by merging MRI and dosimetry data.

Results: Results from an intended interim-analysis made a premature termination necessary. Twenty-two patients were included in the per-protocol analysis. Minimal mean hepatic threshold dose 6 weeks after radiotherapy (primary endpoint) was significantly higher in the study treatment-group compared with the control (19.1 Gy versus 14.6 Gy, $p = 0.011$). Qualitative evidence of fRILI by MRI at 6 weeks was observed in 45.5% of patients in the treatment versus 90.9% of the control group. No significant differences between the groups were observed at the 12-week follow-up.

Conclusions: The post-therapeutic application of PTX, UDCA and low-dose LMWH significantly reduced the extent and incidence fRILI at 6 weeks after radiotherapy. The development of subsequent fRILI at 12 weeks (4 weeks after cessation of PTX, UDCA and LMWH during weeks 1–8) in the treatment group was comparable to the control group thus supporting the observation that the agents mitigated fRILI.

Trial Registration: EU clinical trials register 2008-002985-70 ClinicalTrials.gov NCT01149304

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

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Competing Interests: M. Seidensticker has served as a speaker for Bayer Healthcare and Sirtex medical, and has received research funding from Sirtex medical. R. Seidensticker has served as a speaker for Bayer Healthcare and Sirtex medical, and has received research funding from Sirtex medical. J. Ricke has served as a speaker for Bayer Healthcare and Sirtex medical, and has received research funding from Sirtex medical, Bayer Healthcare and Siemens. M. Pech has served as a speaker for Sirtex medical. B. Sangro has served as a speaker and an advisory board member for Sirtex medical. The authors state herewith that the competing interest as listed above do not alter their adherence to PLOS ONE policies on sharing data and materials.

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Introduction

Highly targeted radiotherapy of liver malignancies has found to be effective in selected patients. Stereotactic radiotherapy, radioembolization using yttrium-90 (^{90}Y) microspheres as well as image-guided brachytherapy (BT) have been described in the literature with promising results [1,2,3]. A key limiting factor of these therapies is the relatively low tolerance of the liver parenchyma to radiation leading to either subclinical focal or generalized injury of the liver parenchyma. When the intensity or the extent of

radiation-induced liver injury (RILI) exceeds the functional reserve, clinical complications appear in the form of radiation (radioembolization) induced liver disease (RILD or REILD) [4,5,6,7]. Prior exposure or concomitant chemotherapy is thought to increase the risk of RILD (or REILD), and as a consequence is a relatively common complication, for example, after conditioning therapy prior to bone marrow transplantation (BMT) [5,8,9,10]. Liver damage whether associated with whole body irradiation or liver-directed radiotherapy have the same pathology, i.e. veno-occlusive disease (VOD) [5,11,12,13].

Medication designed to reduce RILI could improve the safety as well as enable more aggressive radiotherapy. Clinical studies have shown with varying strength of evidence that VOD/RILD after BMT can be ameliorated by pentoxifylline (PTX), ursodeoxycholic acid (UDCA) and low molecular weight heparin (LMWH) [14,15,16,17,18,19,20,21,22] (see Table 1). However, the equivocal nature of the results from most studies probably reflect the heterogeneous study populations (including patients who have received prior chemotherapy or had underlying liver disease) [23]. Thus, a more standardized clinical model is needed to evaluate the protective effects of prophylactic regimens against VOD/RILD.

Image-guided, single-fractioned, high-dose-rate BT of liver malignancies is associated with a well-characterized focal RILI (fRILI), which can be visualized and quantified using functional hepatobiliary magnetic resonance imaging (MRI) (see Figure 1) [6,7]. Importantly, the histopathological evidence of fRILI (i.e. sinusoidal congestion with hepatocyte atrophy and increased reticulin deposits) correlates well with the absence of the hepatocyte uptake of hepatolbiliary MRI contrast media [24]. We have previously found that development of areas of fRILI were maximal at 6–8 weeks post-BT which correlates to the peak incidence of RILD/REILD after conditioning therapy/radioembolization througout the first 2 months post-intervention [5,6,7,25]. We conducted a prospective study to quantify fRILI in patients who were randomized to BT with and without prophylactic PTX, UDCA and low-dose LMWH. To minimize the confounding effects of prior chemotherapy on radiation tolerability, only patients with liver metastases from colorectal cancer (mCRC) were included because these patients tend to have a more consistent pattern of prior exposition to chemotherapy. The cumulative effect of three drugs over a period of 8 weeks [26,27,28] was assessed and patients followed-up at 6 and 12 weeks.

Materials and Methods

The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1.

Study design

This was a prospective, randomised phase II, parallel-group, open-label study conducted at a single centre. The study was approved by the competent authorities (Federal Institute for Drugs and Medical Devices (in german: Bundesinstitut für Arzneimittel und Medizinprodukte - BfArM)) and the local ethics committee (Ethikkommission der Otto-von-Guericke-Universität der Medizinischen Fakultät). Trial registration: Eudra-CT: 2008-002985-70; ClinicalTrials.gov-identifier NCT01149304. Written informed consent was obtained from all patients prior to study entry. Group allocation approach was unrestricted randomization.

Patient characteristics

Consecutive patients (18–80 years) with liver metastases from mCRC, who were scheduled for local ablation with computed-tomography (CT)/MRI-guided BT between 2009 and 2012, were screened (Figure 2). (BT is the local standard ablative treatment in patients ineligible for surgical or all other appropriate intervention).

Women who were pregnant, lactating or of childbearing potential were excluded as were patients with liver cirrhosis, hepatitis B or C, severe coronary artery disease, autoimmune diseases, acute bacterial endocarditis, active major bleedings or high-risk of uncontrolled hemorrhage; severe or moderate renal impairment (GFR <60 mL/min), or known contraindication or hypersensitivity to any of the study treatments or procedures.

Treatment and follow-up

Patients received a single-fraction, CT- or MRI-guided BT of CRC liver metastases (see details below). In those randomized to prophylaxis, the following treatment was initiated during the evening of the day of BT: sc injection of 40 mg q.d. enoxaparin (Clexane, Sanofi Aventis, Paris, France) [20], oral 400 mg t.i.d. PTX (Trental, Sanofi Aventis) [16] and oral 250 mg t.i.d. UDCA (Ursofalk, Falk Pharma, Freiburg, Germany) [17,19]. Patients were discharged usually on the third day post-BT and continued to take study medication at home for 8 weeks. All patients were followed-up on day 3, week 6 and 12 with an optional follow-up at week 24. Within 24 hours of the procedure and at each subsequent visit, blood samples were taken for liver-specific and inflammatory/hemostatic laboratory parameters, and patients were assessed for ECOG-performance status and health-related quality-of-life (using the EQ5D-questionnaire). All adverse reactions related to the study medication or BT were recorded.

Compliance to the prophylactic regimen was evaluated during a dialogue at each visit and the evaluation of anti-Xa-activity at 6 weeks. Insufficient compliance was determined by: either anti-Xa-activity <0.1 IU/mL measured up to 4 hours after last enoxaparin injection, or two dose interruptions of the prophylactic regimen for more than 1 day/week. Non-compliant patients were withdrawn from the per-protocol analysis and study-specific medication stopped.

Image-guided interstitial brachytherapy

The technique of image-guided BT has been described previously [2]. Briefly, the placement of the introducer sheaths (6F Radiofocus, Terumo, Tokyo, Japan) with the BT applicators (Lumencath, Nucletron/Elekta, Veenendaal, The Netherlands) was performed using CT or MRI fluoroscopy. For treatment planning purposes, a spiral CT or T1-weighted MRI of the liver (reconstructed slice thickness: 3 mm) enhanced by intravenous application of iodine contrast media (CT) or Gd-EOB-DTPA (MRI) was acquired.

The high-dose-rate afterloading system (Microselectron, Nucletron/Elekta, Veenendaal, The Netherlands) employed an iridium-192 source with a nominal activity of 10Ci (i.e. 370GBq); decay correction was performed daily. Relative coordinates (x, y, z) of the catheters were determined in the CT/MRI-data set and transferred to the treatment planning system (Oncentra, Nucletron/Elekta). Using these coordinates, the clinical target volume and the predefined minimum dose (20 Gy, delivered as a single fraction [2]), the software calculated a dosimetry and the duration of the iridium-192 source inside the BT catheters. A planning CT with dosimetry is displayed in Figure 1B and F.

Table 1. Summary of published studies on drug treatments for the prevention of VOD/RILD.

Reference	Study design	N	Treatment regimen	Incidence of VOD	p-value*	Bilirubin (μmol/L)	p-value*
Attal et al. 1993 [14]	Prospective RCT	70	**Pentoxifylline** 1,600 mg/d day −8 to day+100 post-BMT	4%	NS	26.4 (mean max)	NS
		70	Control	3%		24.4 (mean max)	
Clift et al. 1993 [22]	Prospective RCT	44	**Pentoxifylline** 2,400 mg/d day −3 to day+70 post-allogeneic BMT	-		26.6 (mean max)	0.62
		44	Control	-		23.47 (mean max)	
Bianco et al. 1991 [16]	Phase 1–2	30	**Pentoxifylline** 1,200, 1,600, and 2,000 mg/d; day −10 to day+100 post-BMT	10%	0.001	-	-
		20	Control (retrospective)	65%		-	
Attal et al 1992 [15]	Prospective RCT	81	**Unfractionated heparin** 100 U/kg/d cont. infusion; day −8 to day+30 post-BMT	2.5%	0.01	7.4% exceeding 34	<0.05
		80	Control	14%		18.7% exceeding 34	
Forrest et al. 2003 (18)	Prospective single-arm	40	**LMWH**: dalteparin 2500 anti-Xa i.u; day −1 to day +30 post-BMT or hospital discharge	22.5%, 2.5% severe			
Or et al. 1996 [20]	Prospective RCT, pilot	61	**LMWH**: enoxaparin 40 mg/day; day+1 to day+40 post-BMT or hospital discharge		0.01	(duration of elevated levels)	0.01
		33	Control				
Essel et al. 1998 [17]	Prospective RCT	34	**UDCA** 600–1200 mg/d; day at least −1 to day +80 post-BMT	15%	0.03	102.6 (mean max)	0.13
		32	Control	40%		188.1 (mean max)	
Ohashi et al. 2000 [19]	Prospective RCT	67	**UDCA** 600 mg/d; day −21 to day+80 post-BMT	3%	0.004	Not reported in detail	NS
		65	Control	18.5%		Not reported in detail	

Table 1. Cont.

Reference	Study design	N	Treatment regimen	Incidence of VOD	p-value*	Bilirubin (µmol/L)	p-value*
Park et al. 2002 [28]	Prospective RCT	82	**UDCA** 600 mg/d + **unfractionated heparin** 5–50 U/kg/d adjusted aPTT of 50 s; day +1 to day +30 post-BMT or hospital discharge (but a minimum of 15d)	16%	0.348	148.8 (mean max)	0.725
		83	**Unfractionated heparin** 5–50 U/kg/d adjusted aPTT of 50 s; day +1 to day +30 post-BMT or hospital discharge (but a minimum of 15d)	19%		173.6 (mean max)	

*Group comparison; LMWH: Low molecular weight heparin; BMT: Bone marrow transplantation; Max: Maximum; NS: Not significant; VOD: Veno-occlusive disease; RCT: Randomized controlled trial; UDCA: ursodeoxycholic acid (ursodiol); aPTT: activated Partial Thromboplastin Time.

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Magnetic resonance imaging

MRI (Achieva 1.5T, Philips, Best, The Netherlands) using the hepatobiliary contrast medium Gd-EOB-DTPA (Primovist, Bayer Healthcare, Leverkusen, Germany) was performed 1 day before and 6 and 12 weeks post-BT. MR-sequence of events was as follows: axial 3D T1-weighted (T1-w) gradient echo THRIVE (T1-High-Resolution-Isotropic-Volume-Excitation) (Time-to-Echo/Time-to-Repetition 4/10 ms, flip-angle 10°) with fat-suppression pre-contrast, at 20 s, 60 s and 120 s and 20 minutes after iv 0.1 mL/kg bodyweight Gd-EOB-DTPA. The slice thickness was 3 mm. For the study-specific MRI volumetry, dynamic THRIVE at 60 s (for the exclusion of tumor progression/local recurrence) and hepatobiliary phase THRIVE 20 min after application of Gd-EOB-DTPA (for the determination of area of fRILI) were mandatory.

Identification of the radiation isodose (minimal hepatic threshold dose) that demarcated the border between the fRILI and functioning liver tissue (as defined by non-uptake and uptake of Gd-EOB-DTPA enhanced MRI, respectively) was performed as follows in a blinded matter.

The hepatobiliary phase THRIVE was transferred to the BT-planning software. Image registration of the hepatobiliary phase THRIVE to the contrast-enhanced planning CT/MRI (including the dosimetry) was performed by an isoscalar local semi-automated point-based 3D-3D image registration using predefined match points (3 or 4 corresponding landmarks restricted to liver structures). Registration was only accepted if the target area merged perfectly by visual assessment. As a result of this procedure, the software simultaneously displayed the treatment dosimetry and anatomical structures/fRILI of the hepatobiliary phase THRIVE. The volume of the liver parenchyma with radiation-induced impaired uptake of Gd-EOB-DTPA (i.e. fRILI) was determined. The isodose of the dosimetry encircling this volume was determined at five different axial levels and the mean of these values recorded. This dose resembles the dose which was formerly applied at the now demarcated rim of the fRILI, corresponding to the assumed minimal hepatic tolerance dose. To ensure a negligible registration error, the volume of fRILI was inserted into the dose-volume-histogram of the dosimetry. The corresponding isodose was stored. Results of the two methods showed a high correlation of 0.899 and 0.562 ($p<0.001$ and $p=0.006$) for 6 and 12 weeks, respectively. To minimize methodological errors, the mean isodose value of the two methods was taken. In case of more than one treated lesion, the mean of the determined isodoses was used. If no detectable fRILI was seen in follow-up, the minimal mean hepatic threshold dose was defined as the dose which was previously administered at the tumor margin (since an effect on the liver parenchyma above this dose level cannot be excluded). Figure 1 illustrates the development and appearance of the fRILI in hepatobiliary phase THRIVE.

Endpoints and statistical analyses

The aim of the study was to assess if a combination regimen of PTX, UDCA and low-dose LMWH for 8 weeks provided a preventive effect regarding irradiation damage to liver parenchyma (as resembled by the minimal mean threshold dose of the fRILI volume) at 6 weeks (primary endpoint) and at 12 weeks (secondary endpoint) after BT.

As additional descriptor, detectable fRILI in Gd-EOB-DTPA MRI (yes/no) was recorded at each follow-up. Further secondary objectives included the safety of the study treatment after BT including changes in bilirubin and albumin which were graded according to Common Terminology Criteria for Adverse Events version 3 (CTCAE3.0).

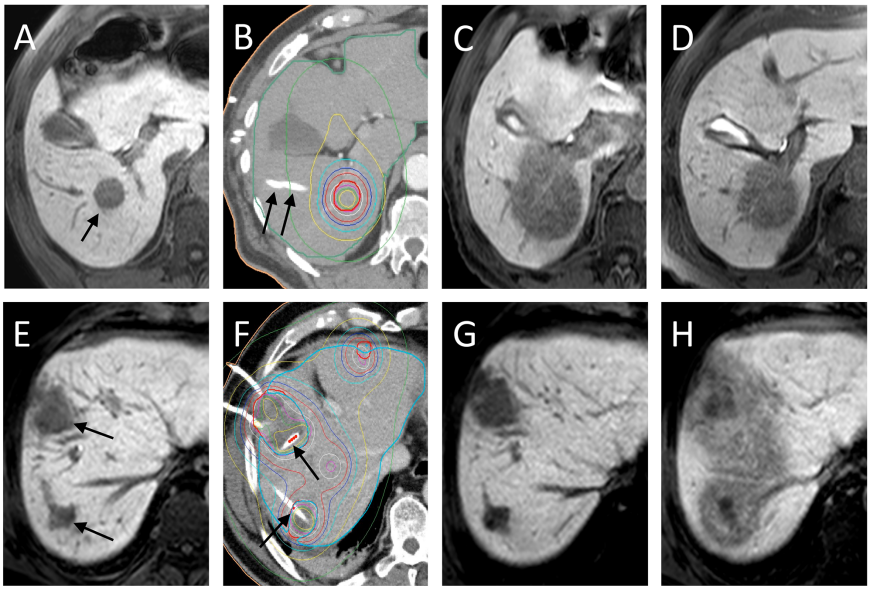

Figure 1. T1w-axial THRIVE 20 min after application of Gd-EOB-DTPA (A, C–E and G, H) and BT planning CT with dosimetry (B and F). A–D, control group. A: pre-treatment MRI displaying a metastasis scheduled for BT treatment (black arrow). B: Planning-CT after introduction of the brachytherapy catheters (black arrows). Clinical target volume (CTV) represented by bold red circle and dosimetry by coloured lines (red: 20 Gy-, blue: 12 Gy-isodose). C: MRI at 6 weeks showing substantial reduction in Gd-EOB-DTPA uptake by liver parenchyma adjacent to treated metastases (i.e. focal radiation-induced liver injury, fRILI). Note: The area of fRILI matches the geometry of the dosimetry (B). Determined threshold dose: 9.75 Gy. D: MRI at 3 months showing shrinkage of the fRILI. Determined threshold dose: 11.9 Gy. E–H, treatment group. E: pre-treatment MRI displaying two metastases (black arrow); two more treated lesions are not displayed in the plane. F: Planning-CT (annotations: see B). G: MRI at 6 weeks showing no fRILI. H: MRI at 3 months after radiotherapy (and 1 month after finishing study treatment) showing a substantial region of fRILI. Determined threshold dose: 15.8 Gy.
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The relation between hepatocyte dysfunction and changes in the following liver-specific and inflammatory/hemostatic laboratory values were analysed: fibrinogen, factor-VIII-activity, interleukin-6, protein-C-activity, protein-S-activity, von-Willebrand-factor-activity and antithrombin-III-activity [29].

Determination of sample size was based on the expected minimum between-group difference of 2.1 Gy (SD 2.3 Gy) for minimal mean hepatic threshold dose at 6 weeks after BT (from 9.9 Gy to 12 Gy) [7]. A sequential test with 2 stages according to the Pocock-design was used which yielded a total of 22 observations per group with a scheduled interim analysis after 11 observations per group when $a = 0.025$ and power $1\text{-}b = 0.8$. Interim-analysis showed a significant difference between the groups regarding the primary variable with a one-sided p-value of 0.011. A one-sided p of <0.0148 was necessary to terminate the study prematurely.

Statistical analysis was performed using SPSS (SPSS21, IBM, Chicago, Il, USA). Descriptive analysis of patient characteristics and laboratory findings was performed. The primary analysis was evaluated in the per protocol cohort and repeated in the intention-to-treat population as sensitivity analysis. Between-group differences in minimal mean hepatic threshold after BT at 6 and 12 weeks were compared using a two-sample *t*-tests, and evidence of detectable fRILI were compared using the Fisher's-exact-test. Possible confounding factors were evaluated using the Mann-Whitney-*U*-test for metric variables and the Fisher's-exact-test for categorical variables, and then between-group differences for the primary endpoint were evaluated with inclusion of the covariables (ANOVA and ANCOVA). The relationship between the minimal mean hepatic threshold dose and laboratory values was tested by Pearson's correlation and ANCOVA. Group comparison regarding ECOG and EQ5D was made by Mann-Whitney-*U*-test. Median overall survival was estimated by Kaplan-Meier (group comparison by log-rank test). A p-value of <0.05 was statistically significant.

Results

Of 129 patients screened with liver metastases from colorectal cancer scheduled for BT, 30 patients were included in the study and 22 patients (11 per group) in the primary analyses of the per-protocol group (see CONSORT diagram, Figure 2). Demographic characteristics of randomized patients at screening are summarized in Table 2 and the baseline liver function and other laboratory parameters are presented in Table 3. Group comparison revealed a similar distribution of possible confounders. A tendency towards a larger volume of significantly radiation exposed liver parenchyma (>10 Gy) in the study treatment group (Table 2) may have potentially lowered the hepatic tolerance dose in this group instead of increase it [25].

The minimal mean hepatic threshold dose at 6 weeks after BT (primary endpoint) was significantly higher in the study treatment group than the control (19.1 Gy versus 14.6 Gy, $p = 0.011$, Table 4) with comparable results with the intention-to-treat analysis (Table 4). Correspondingly, fewer patients in the study treatment group than the control had evidence of fRILI at 6 weeks (45.5% versus 90.9%); this difference was also significant in the intention-to-treat analysis (Table 4). However at 12 weeks after BT (and 4 weeks after cessation of study treatment), these between-group differences were not observed (in neither the per-protocol nor intention-to-treat analyses) for the minimal mean hepatic threshold dose and the proportion of patients with fRILI (Table 4). Results from the optional follow-up at 24 weeks after BT continually showed no between-group differences for the minimal

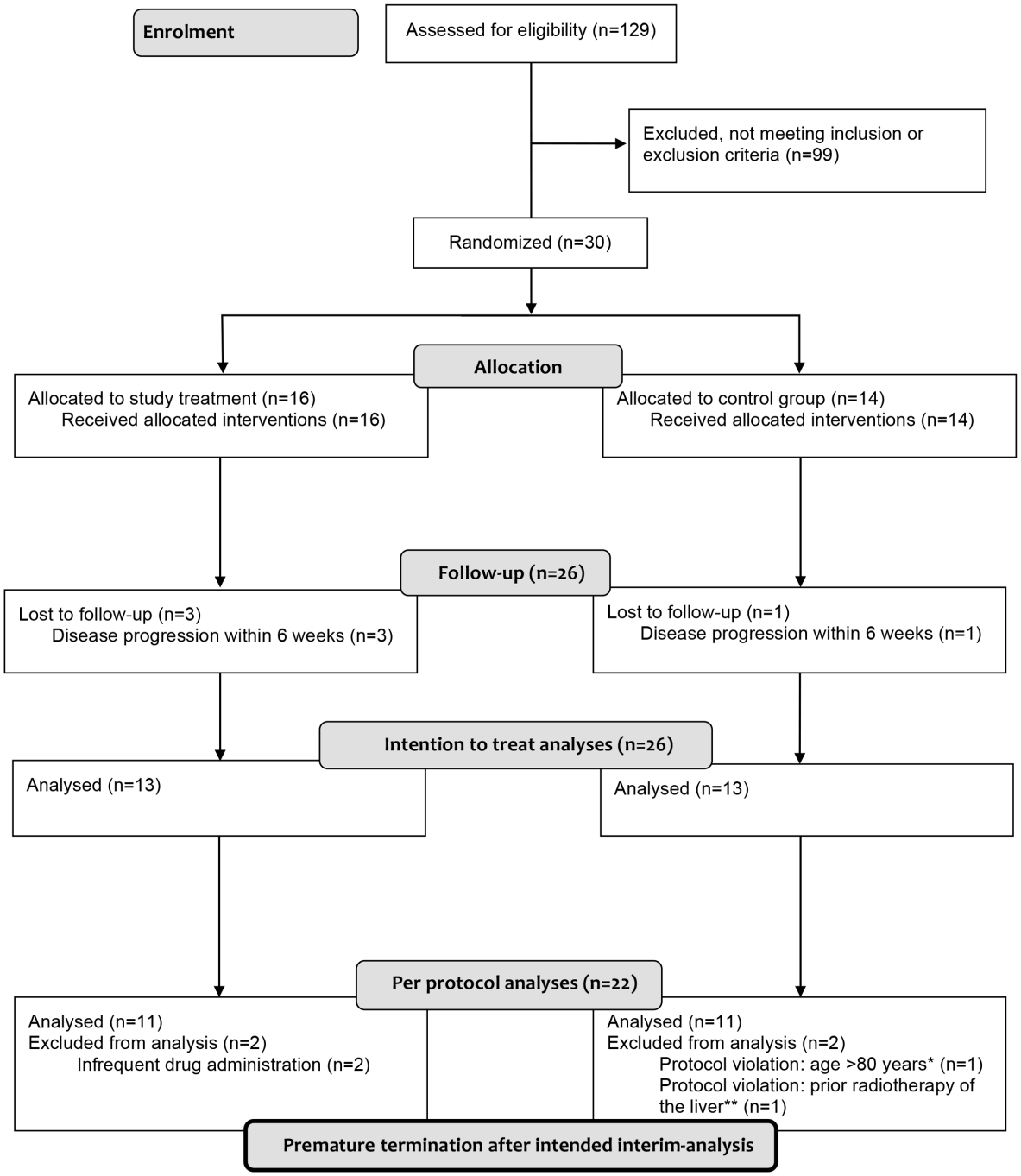

Figure 2. CONSORT-diagram. *Exclusion criterion age was initially disregarded by error in this patient (aged 82). **Exclusion criterion prior radiotherapy was initially disregarded by error in this patient (prior radiotherapy was performed 2 years earlier with location in the contralateral liver lobe).
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mean hepatic threshold dose and the proportion of patients with fRILI (no change of the proportion of patients with fRILI as compared to 12 weeks follow-up; the minimal mean hepatic threshold dose for treatment group was 20.1 Gy (1 patient missing) and for the control group 21.0 Gy; $p>0.05$, per-protocol analysis (with comparable results with the intention-to-treat analysis)).

Covariate analyses also showed no influence of recorded covariables on the primary endpoint; only group allocation was significant (Table 5).

EQ5D (as a descriptor of quality of life) and distribution of ECOG performance status were not significantly different at baseline (Table 2) or at any follow-up visit (Table S1). Median overall survival from time of BT on was not different between the groups with 30.0 months (95%CI: 8.7–51.3) in the treatment group and 39.5 months (27.5–51.5) in the control group ($p = 0.430$).

Safety analyses were conducted in all 30 patients who received BT. The following mild-to-moderate adverse events CTCAEv3 grade 1–2 were reported (in the treatment/control groups) on day

Table 2. Patient characteristics (per protocol analysis).

Variable	Treatment group (n = 11)	Control (n = 11)	p-value (between group)*
Sex (m/f)	9/2	8/3	1.000
Age (years)	71.09±5.47	65.09±12.55	0.408
Weight (kg)	84.64±11.68	83.91±12.89	0.592
Height (cm)	174.09±6.79	172.64±6.90	0.834
ECOG at baseline (0/1/2)	6/4/1	4/5/2	0.370
EQ5D visual analogue score	72.36±14.56	76.36±13.02	0.446
History of liver surgery	45.5%	45.5%	1.000
Steatosis hepatis	36.4%	18.2%	0.635
Diabetes mellitus	18.2%	27.3%	1,000
Chemotherapy pretreatment			
Applied lines	1.00±0.63	1.00±0.45	1.000
no chemotherapy	18.2%	9.1%	NA
1 line	63.6%	81.8%	0.672
2 lines	18.2%	9.1%	NA
Prior chemotherapy			
Oxaliplatin	63.6%	63.6%	1.000
Irinotecan	36.4%	36.4%	1.000
Biologicals	54.5%	54.5%	1.000
Number of treated metastases	1.91±1.04	1.45±0.52	0.382
Maximum diameter of metastases (mm)	37.18±12.91	29.45±11.79	0.146
Clinical target volume (cm^3)	42.82±29.26	31.36±37.14	0.156
Number of used brachytherapy catheters	3.18±1.78	2.27±1.74	0.079
Liver volume (cm^3)	1296.1±226.6	1451.3±278.6	0.401
Interval between BT and 6 weeks FU (days)	43.91±4.76	45.09±4.68	0.757
Interval between BT and 3 months FU (days)	87.34±4.52	89.55±6.15	0.505
Liver volume with a dose exposure >10 Gy (%)	22.55±14.45	11.95±10.43	0.056
Chemotherapy during follow-up	18.2%	9.1%	1.000

Continuous data: mean ± standard deviation, frequencies: counts or percent.
*Group comparison, continuous data compared by Mann-Whitney U test, frequency data compared by Pearson's chi square test.
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3 after BT: pain (1 patient/1 patient) and fatigue (0/1); at week 6: pain (2/0), fatigue (0/1), nausea (1/0) and diarrhea (2/0); nausea and diarrhea was probably related to PTX or UDCA. One grade 3 subacute bleeding episode from the bile duct, related to BT, occurred in the study treatment group which was successfully managed by endoscopic coagulation.

Analysis of the laboratory data revealed no grade 3/4 changes in bilirubin or albumin. One grade 1 reduction of albumin in the treatment group at 6 weeks was unchanged at week 12. One patient in control group with elevated (grade 1) bilirubin at baseline remained stable throughout follow-up. RILD was not observed on either group.

Laboratory analysis regarding liver-specific and inflammatory/hemostatic parameters found no relevant findings at baseline (Table 3). At week 6, slightly higher gamma-glutamyl-transferase levels and protein-S-activity were recorded in the control group compared with the treatment group. At 6 and 12 weeks, there was slight but significant mean decrease from baseline in cholinesterase in the treatment group. Additionally, mean fibrinogen and von-Willebrand-factor-activity increased significantly from baseline in the treatment group at 6 and 12 weeks; while significant increases from baseline were recorded with mean fibrinogen, factor-VIII-activity and aspartate-transaminase in the control group at 6 weeks.

No correlation between the minimal mean hepatic threshold and liver-specific and inflammatory/hemostatic laboratory values was found at either week 6 or 12 (data not shown).

Discussion

In this prospective study, we were able to show a significant reduction in fRILI (as measured by hepatobiliary MRI) at 6 weeks after BT of colorectal liver metastases in patients who received low-dose LMWH, PTX and UDCA. Re-assessment of patients at 12 weeks (4 weeks after cessation of study treatment) found that the extent and incidence of fRILI was comparable to the control group, thereby supporting the reliability of our findings. This is further authenticated by the results of the (optional) 24 weeks follow-up. According to our results we believe that we were able to mitigate rather than delay the fRILI by the prophylactic regimen. The finding that the positive effect of the medication to the liver parenchyma as seen at the 6 weeks follow-up vanished after discontinuation of the medication (after 8 weeks) in the 3 months

Table 3. Laboratory parameters at baseline and follow-up (per protocol analysis).

Variable (normal range)		Treatment group (n = 11)	Control (n = 11)	p-value (between group)*	p-value (baseline *vs.* follow-up)**
Bilirubin	baseline	8.27±2.92	8.39±5.61	0.594	
(<21.0 μmol/L)	6 weeks	9.58±9.94	9.56±7.18	0.641	0.182 (0.350)
	12 weeks	8.71±4.27	8.75±5.95	0.735	0.594 (0.505)
Albumin	baseline	44.21±3.46	44.05±2.45	0.833	
(35.0–52.0 g/L)	6 weeks	42.49±5.16	42.67±3.17	0.743	0.197 (0.060)
	12 weeks	42.84±4.94	43.66±2.31	0.743	0.212 (0.332)
Cholinesterase	baseline	149.26±47.97	144.73±21.73	0.718	
(88–215 μmol/s.L)	6 weeks	136.27±51.65	143.82±29.10	0.433	**0.023** (0.929)
	12 weeks	132.94±49.22	153.36±30.96	0.088	**0.010** (0.423)
Aspartate transaminase	baseline	0.56±0.18	0.46±0.17	0.211	
(0.17–0.83 μmol/s.L)	6 weeks	0.59±0.17	0.55±0.23	0.533	0.373 (**0.016**)
	12 weeks	0.63±0.47	0.54±0.17	0.974	0.563 (0.056)
Alanine transaminase	baseline	0.44±0.20	0.51±0.36	1,000	
(0.17–0.83 μmol/s.L)	6 weeks	0.50±0.18	0.62±0.45	0.742	0.443 (0.109)
	12 weeks	0.53±0.43	0.52±0.27	0.718	0.508 (0.722)
Gamma glutamyltransferase	baseline	1.61±2.62	1.49±1.21	0.189	
(0.17–1.19 μmol/s.L)	6 weeks	0.82±0.83	2.21±1.71	**0.011**	0.100 (0.050)
	12 weeks	1.25±1.17	1.97±1.49	0.139	0.722 (0.306)
Glutamate dehydrogenase	baseline	104.36±91.47	108.82±94.84	0.844	
(<120 nmol/s.L)	6 weeks	67.55±31.43	123.27±105.88	0.490	0.328 (0.308)
	12 weeks	128.11±108.79	126.09±95.19	0.849	0.674 (0.374)
International normalized	baseline	93.9±3.03	95.55±2.98	0.053	
ratio (0.85–1.27)	6 weeks	94.11±2.71	94.8±2.44	0.399	0.438 (0.502)
	12 weeks	94.63±2.50	95.33±3.61	0.732	0.334 (0.498
Interleukin 6	baseline	4.54±3.31	3.71±3.09	0.245	
(<7.0 pg/mL)	6 weeks	8.44±8.53	7.62±4.41	0.809	0.266 (0.038)
	12 weeks	10.50±9.24	4.06±2.42	0.229	0.139 (0.515)
Fibrinogen	baseline	3.72±0.53	3.99±0.46	0.377	
(1.50–4.00 g/L)	6 weeks	4.50±1.17	4.77±0.84	0.365	**0.014** (**0.017**)
	12 weeks	4.65±1.04	4.23±0.49	0.416	**0.037** (0.214)
Factor VIII activity	baseline	169.09±41.51	160.60±42.12	0.756	
(70–150%)	6 weeks	195.45±61.02	218.91±60.77	0.490	0.130 (0.093)
	12 weeks	199.7±67.26	257.09±150.23	0.360	0.169 (**0.017**)
Protein C activity	baseline	107.36±33.99	109.70±12.46	0.145	
(>70%)	6 weeks	108±32.68	106.55±18.67	0.767	0.799 (0.475)
	12 weeks	101.5±27.26	114±19.76	0.084	0.113 (0.540)
Protein S activity	baseline	85.36±12.26	86.80±12.55	0.848	
(>60%)	6 weeks	82.18±15.16	104.36±27.09	**0.036**	0.266 (0.086)
	12 weeks	87.3±14.54	91±10.6	0.549	0.799 (0.507)
von Willebrand factor	baseline	164.09±42.81	174.90±71.14	0.973	
activity (70–130%)	6 weeks	222.27±59.75	201.73±71.76	0.554	**0.013** (0.075)
	12 weeks	209.5±77.35	215.27±75.31	0.883	**0.013** (0.333)
Antithrombin III activity	baseline	92.73±13.72	98.90±11.50	0.191	
(>80%)	6 weeks	96.73±15.31	98.2±9.78	0.944	0.082 (0.779)
	12 weeks	96.4±12.08	96.73±9.51	0.751	0.407 (0.681)

*Between group comparison, Mann-Whitney U test;
**Comparison versus baseline (in brackets p-value of control group), Wilcoxon test.
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Table 4. Minimal mean hepatic tolerance dose (Gy) and evidence of detectable focal radiation-induced liver injury (fRILI) after BT, group comparison.

Variable	Group			p-value (between groups)
Minimal mean hepatic tolerance dose (primary endpoint)		**Dose (Gy)**	**SD**	
At 6 weeks	Control	14.64 [14.15]	4.01 [3.93]	
	Treatment	19.06 [18.46]	3.35 [3.59]	**0.011** [**0.007**]
At 12 weeks	Control	16.38 [16.10]	3.57 [3.60]	
	Treatment	19.04 [18.50]	2.88 [3.11]	0.069 [0.082]
Detectable fRILI		**Counts**	**Frequency**	
At 6 weeks	Control	10 [12]	90.9% [92.3%]	
	Treatment	5 [7]	45.5% [53.8%]	**0.022** [**0.027**]
At 12 weeks	Control	10 [12]	90.9% [92.3%]	
	Treatment	10 [12]	90.9% [92.3%]	1.000 [1.000]

Per protocol analysis (n = 22); Intention-to-treat analysis (n = 26) in square brackets.
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follow-up, make us believe that the fRILI was in fact mitigated in that period. Further on, the extent of the fRILI at 6 weeks in the treatment group and at 3 months (and 6 months) in both groups was less in size compared to the fRILI in the control group at 6 weeks (the peak of the fRILI in our study). Thus, the maximum extent of the fRILI at 6 weeks was skipped in the treatment group as compared to the control group. However, the radiation damage could not be suppressed completely by the prophylactic regimen with a rebound after cessation of the treatment to the level of the control group in later follow-ups. Thus, it is possibly right to assume additionally a delay on the development of the fRILI by the prophylactic regimen. This delay is considered to be advantageous as well since a rapid formation of the fRILI can be delayed (and mitigated) allowing the liver remnant to compensate for the fRILI. However, although appropriately powered, the study should be understood as a pilot due to the small sample size. To compensate for the rebound of the fRILI after cessation of the prophylactic regimen and for a better understanding of the dynamics of the fRILI, a study concept with a prolonged course for the prophylactic regimen is planned.

RILI remains a challenge in the treatment of liver malignancies by radiotherapy (whether percutaneous, interstitial or by radio-embolization) because it may eventually translate into RILD or REILD. Further on, life-threatening VOD associated with combined-modality induced liver disease occurs in 5–60% of patients undergoing BMT [18,23,26]. For this reason, the potentially protective effects of a number of treatments including low-dose LMWH, PTX and UDCA have been evaluated. Although the efficacy appears equivocal in some studies [14,15,16,17,18,19,20,21,28] (Table 1), we determined that the combination of low-dose LMWH, PTX and UDCA appeared to be the most promising option for further evaluation with BT. We believe that our success in showing a benefit in ameliorating fRILI with this combination is based on the following factors: a highly homogeneous patient cohort; attention to patient compliance to the prophylactic regimen; and direct measurement of damage to the liver parenchyma rather than clinical endpoints.

The treatment course of 8 weeks for the medication was determined on the assumption that occurrence of RILD and fRILI peaks around 2 months after radiation-exposure [5,6,7,25]. However, our findings suggest that the radiation-induced injury to the liver structures and cell endothelial continues beyond 8 weeks and that discontinuation of the medication at this time allows the development of a veno-occlusive state/liver cell dysfunction. Endothelial cell damage, which triggers local thrombotic mechanisms, leading to microvascular flow insufficiency, production of cytotoxic substances, and ultimately hepatocellular necrosis, has been thought to be an early event in the development of RILD/VOD [5,10,11,30,31]. The current evidence indicates that PTX, low-dose LMWH and UDCA may act through a variety of mechanisms to alleviate these effects. PTX, for example, down regulates tumor-necrosis factor-α (TNF-α), a prime suspect in either the initiation or amplification of tissue injury following radiation. PTX also stimulates vascular endothelial production of non-inflammatory prostaglandins of the E- and I-series, enhancing loco-regional blood flow and promoting thrombolysis [16].

LMWHs are assumed to prevent subsequent thrombosis of hepatic venules after endothelial damage and therefore decrease the risk of VOD/RILD [18].

By oral administration of UDCA the concentration of potentially liver toxic hydrophobic bile acids can be reduced [32]. Several *in vitro* studies suggest that potential attenuating effects of UDCA on the pathogenesis of VOD is achieved through the down-regulation of inflammatory cytokine such as TNF-α and interleukin-1 [33]. These cytokines not only induce and amplify liver damage but are also associated with apoptosis in endothelial cells [34] and the development of VOD. UDCA also appears to have a direct effect on programmed-cell death, inhibiting apoptosis and protecting against the membrane damaging effects associated with hydrophobic bile acids in both hepatocytes and non-liver cells [35].

The rationale for this combined treatment approach is based on the assumption that LMWH, PTX and UDCA, which act through a variety of different mechanisms, may act synergistically or in a complimentary fashion to protect the liver [26,27,28]; although further study is needed to fully evaluate this hypothesis. However, based on the low toxicity profile of these medications, we believe

Table 5. Covariate analysis of minimal mean hepatic tolerance dose 6 weeks after BT (per protocol, n = 22).

Covariate*	p-value (group influence)	p-value (co-variate influence)
Sex (m/f)	**0.015**	0.458
Age (y)	**0.016**	0.864
Weight (kg)	**0.010**	0.117
Height (cm)	**0.011**	0.485
ECOG at baseline (0 and 1 vs 2)	**0.008**	0.310
EQ5D visual analogue score	**0.015**	0.868
History of liver surgery	**0.007**	0.064
Steatosis hepatis	**0.014**	0.845
Diabetes mellitus	**0.015**	0.627
Chemotherapy pre treatment	**0.012**	0.373
Used chemotherapeutic agents		
Oxaliplatin	**0.013**	0.991
Irinotecan	**0.011**	0.327
Biologicals	**0.012**	0.459
Number of treated metastases	**0.013**	0.681
Maximum diamter of metastases (mm)	**0.023**	0.669
Clinical target volume (cm^3)	**0.013**	0.815
Liver volume (cm^3)	**0.018**	0.937
Interval from BT to 6 weeks FU (days)	**0.008**	0.258
Liver volume with a dose exposure >10 Gy (%)	**0.013**	0.598
Chemotherapy during follow-up	**0.015**	0.191
Bilirubin baseline	**0.030**	0.401
Albumin baseline	**0.020**	0.784
Aspartate transaminase baseline	**0.025**	0.263
Alanine transaminase baseline	**0.006**	0.092
Cholinesterase baseline	**0.013**	0.425
Gamma glutamyltransferase baseline	**0.012**	0.317
Glutamate dehydrogenase baseline	**0.011**	0.352
International normalized ratio baseline	**0.008**	0.783
Interleukin 6 baseline	**0.030**	0.401
Fibrinogen baseline	**0.002**	0.232
Factor VIII activity baseline	**0.005**	0.615
Protein C activity baseline	**0.004**	0.868
Protein S activity baseline	**0.004**	0.831
von Willebrand factor activity baseline	**0.004**	0.763
Antithrombin III activity baseline	**0.008**	0.261

*Two-way ANOVA for categorical factors, ANCOVA for metric covariables.

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that this initial approach can be justified. Although the patient numbers are small, the absence of severe toxicities acccords with experience of other published data [15,16,17,19,20,21,28].

Regarding changes of laboratory values, no clinically relevant (grade 3/4) toxicities were observed. The observed slight increases (varying over time and group) of fibrinogen, factor-VIII-activity, protein-S-activity and von-Willebrand-factor-activity correspond most likely to an unspecific increase in acute-phase proteins after radiotherapy or/and to a consequence of radiation-induced endothelial damage of the hepatic veins and sinuses with subsequent platelet aggregation. Regarding the course of liver specific laboratory paramters after BT, it might be argued that the induced fRILI was possibly too small to induce a significant overall increase of these parameters. However, the slight but significant increase of aspartate transaminase in the control group indicates a parenchymal damage. Interestingly, this increase was not seen in the treatment group, indicating a decreased parenchymal damage under preventive medication.

The primary endpoint in our analysis is based on a surrogate i.e. fRILI visualized and quantified using hepatobiliary contrast agent (Gd-EOB-DTPA)-enhanced MRI. Hepatobiliary contrast agents differ from other gadolinium chelates in that they are selectively taken up by functioning hepatocytes through an organic-anion-transporter-polypeptide (mainly OATP1B1 and 3) and excreted

into the bile by the multidrug-resistance-protein-2. For Gd-EOB-DTPA, the biliary excretion rate is approximately 50% in humans [36,37]. Regardless of the mechanism of damage to liver, the hepatobiliary contrast media in functionally altered liver parenchyma is significantly reduced [38]. This is also true for fRILI since a loss of uptake of hepatobiliary contrast media is clearly evident in the liver parenchyma adjacent to the clinical target volume after local radiotherapy (Figure 2) [6,7]. Importantly, an agreement has been found between the histopathological evidence of fRILI/VOD and loss of hepatocellular uptake of hepatobiliary contrast agent [24].

Unlike the reduced uptake of hepatobiliary contrast agents in sinusoidal-obstruction-syndrome observed after platinum-containing chemotherapy (which is reticular in geometry and generalized all over the liver) [39], the reduced uptake of hepatobiliary contrast media after BT is focal, homogenous and circumferential around the clinical target volume (Figure 1) [6,7]. Thus, we believe that we can exclude underlying sinusoidal-obstruction-syndrome as a confounder of our results. Additionally, the history of platinum-containing chemotherapy was equal between the groups and without influence on the endpoint.

We suggest that our study results can be transferred to other established radiation treatment methods of liver malignancies such as ^{90}Y-radioembolization. According to conversion calculations, the dose ranges in the liver parenchyma associated with ^{90}Y-radioembolization and BT are comparable, if re-calculated with respect to the standard fractionation. We therefore hypothesize that preventive treatment approaches against RILD/REILD should be equally effective for both ^{90}Y-radioembolization and BT.

Conclusions

In summary, our results show a highly significant reduction in fRILI after BT of colorectal liver metastases in patients who received low-dose LMWH, PTX and UDCA. Further on, we believe that these findings can be adopted for the prevention of radiation-induced liver damage after other radiotherapeutic approaches as ^{90}Y-radioembolization and that further clinical studies in this area are warranted.

Supporting Information

Table S1 ECOG, EQ5D dimensions and EQ5D VAS, baseline and follow-up; group comparison (per-protocol only).
(DOCX)

Checklist S1 Consort Checklist regarding the present study.
(DOCX)

Protocol S1 Study protocol as submitted to the competent authorities.
(PDF)

Author Contributions

Contributed to the writing of the manuscript: MS PW JR. Statistical planning and analysis: SK RD MS. Conceived and designed the experiments: MS RS RD BS JR. Performed the experiments: MS RS RD PH GG JR. Analyzed the data: MS RD KM MP RS SK. Contributed reagents/materials/analysis tools: PH GG SK.

References

1. Boda-Heggemann J, Dinter D, Weiss C, Frauenfeld A, Siebenlist K, et al. (2012) Hypofractionated image-guided breath-hold SABR (stereotactic ablative body radiotherapy) of liver metastases–clinical results. Radiation oncology 7: 92.
2. Ricke J, Mohnike K, Pech M, Seidensticker M, Ruhl R, et al. (2010) Local response and impact on survival after local ablation of liver metastases from colorectal carcinoma by computed tomography-guided high-dose-rate brachytherapy. International journal of radiation oncology, biology, physics 78: 479–485.
3. Seidensticker R, Denecke T, Kraus P, Seidensticker M, Mohnike K, et al. (2012) Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovascular and interventional radiology 35: 1066–1073.
4. Emami B, Lyman J, Brown A, Coia L, Goitein M, et al. (1991) Tolerance of normal tissue to therapeutic irradiation. International journal of radiation oncology, biology, physics 21: 109–122.
5. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, et al. (1995) Hepatic toxicity resulting from cancer treatment. International journal of radiation oncology, biology, physics 31: 1237–1248.
6. Ricke J, Seidensticker M, Ludemann L, Pech M, Wieners G, et al. (2005) In vivo assessment of the tolerance dose of small liver volumes after single-fraction HDR irradiation. International journal of radiation oncology, biology, physics 62: 776–784.
7. Seidensticker M, Seidensticker R, Mohnike K, Wybranski C, Kalinski T, et al. (2011) Quantitative in vivo assessment of radiation injury of the liver using Gd-EOB-DTPA enhanced MRI: tolerance dose of small liver volumes. Radiation oncology 6: 40.
8. McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED (1985) The clinical course of 53 patients with venocclusive disease of the liver after marrow transplantation. Transplantation 39: 603–608.
9. Sangro B, Gil-Alzugaray B, Rodriguez J, Sola I, Martinez-Cuesta A, et al. (2008) Liver disease induced by radioembolization of liver tumors: description and possible risk factors. Cancer 112: 1538–1546.
10. Farthing MJ, Clark ML, Sloane JP, Powles RL, McElwain TJ (1982) Liver disease after bone marrow transplantation. Gut 23: 465–474.
11. Fajardo LF, Colby TV (1980) Pathogenesis of veno-occlusive liver disease after radiation. Archives of pathology & laboratory medicine 104: 584–588.
12. Reed GB, Jr., Cox AJ, Jr (1966) The human liver after radiation injury. A form of veno-occlusive disease. The American journal of pathology 48: 597–611.
13. Shulman HM, Gown AM, Nugent DJ (1987) Hepatic veno-occlusive disease after bone marrow transplantation. Immunohistochemical identification of the material within occluded central venules. The American journal of pathology 127: 549–558.
14. Attal M, Huguet F, Rubie H, Charlet JP, Schlaifer D, et al. (1993) Prevention of regimen-related toxicities after bone marrow transplantation by pentoxifylline: a prospective, randomized trial. Blood 82: 732–736.
15. Attal M, Huguet F, Rubie H, Huynh A, Charlet JP, et al. (1992) Prevention of hepatic veno-occlusive disease after bone marrow transplantation by continuous infusion of low-dose heparin: a prospective, randomized trial. Blood 79: 2834–2840.
16. Bianco JA, Appelbaum FR, Nemunaitis J, Almgren J, Andrews F, et al. (1991) Phase I-II trial of pentoxifylline for the prevention of transplant-related toxicities following bone marrow transplantation. Blood 78: 1205–1211.
17. Essell JH, Schroeder MT, Harman GS, Halvorson R, Lew V, et al. (1998) Ursodiol prophylaxis against hepatic complications of allogeneic bone marrow transplantation. A randomized, double-blind, placebo-controlled trial. Annals of internal medicine 128: 975–981.
18. Forrest DL, Thompson K, Dorcas VG, Couban SH, Pierce R (2003) Low molecular weight heparin for the prevention of hepatic veno-occlusive disease (VOD) after hematopoietic stem cell transplantation: a prospective phase II study. Bone marrow transplantation 31: 1143–1149.
19. Ohashi K, Tanabe J, Watanabe R, Tanaka T, Sakamaki H, et al. (2000) The Japanese multicenter open randomized trial of ursodeoxycholic acid prophylaxis for hepatic veno-occlusive disease after stem cell transplantation. American journal of hematology 64: 32–38.
20. Or R, Nagler A, Shpilberg O, Elad S, Naparstek E, et al. (1996) Low molecular weight heparin for the prevention of veno-occlusive disease of the liver in bone marrow transplantation patients. Transplantation 61: 1067–1071.
21. Ruutu T, Eriksson B, Remes K, Juvonen E, Volin L, et al. (2002) Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. Blood 100: 1977–1983.
22. Clift RA, Bianco JA, Appelbaum FR, Buckner CD, Singer JW, et al. (1993) A randomized controlled trial of pentoxifylline for the prevention of regimen-related toxicities in patients undergoing allogeneic marrow transplantation. Blood 82: 2025–2030.
23. McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED (1984) Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology 4: 116–122.
24. Seidensticker M, Burak M, Kalinski T, Garlipp B, Koelble K, et al. (2014) Radiation-Induced Liver Damage: Correlation of Histopathology with Hepatobiliary Magnetic Resonance Imaging, a Feasibility Study. Cardiovascular and interventional radiology.

25. Wybranski C, Seidensticker M, Mohnike K, Kropf S, Wust P, et al. (2009) In vivo assessment of dose volume and dose gradient effects on the tolerance dose of small liver volumes after single-fraction high-dose-rate 192Ir irradiation. Radiation research 172: 598–606.
26. Shulman HM, Hinterberger W (1992) Hepatic veno-occlusive disease–liver toxicity syndrome after bone marrow transplantation. Bone marrow transplantation 10: 197–214.
27. Lakshminarayanan S, Sahdev I, Goyal M, Vlachos A, Atlas M, et al. (2010) Low incidence of hepatic veno-occlusive disease in pediatric patients undergoing hematopoietic stem cell transplantation attributed to a combination of intravenous heparin, oral glutamine, and ursodiol at a single transplant institution. Pediatric transplantation 14: 618–621.
28. Park SH, Lee MH, Lee H, Kim HS, Kim K, et al. (2002) A randomized trial of heparin plus ursodiol vs. heparin alone to prevent hepatic veno-occlusive disease after hematopoietic stem cell transplantation. Bone marrow transplantation 29: 137–143.
29. Lee JH, Lee KH, Kim S, Lee JS, Kim WK, et al. (1998) Relevance of proteins C and S, antithrombin III, von Willebrand factor, and factor VIII for the development of hepatic veno-occlusive disease in patients undergoing allogeneic bone marrow transplantation: a prospective study. Bone marrow transplantation 22: 883–888.
30. Catani L, Gugliotta L, Vianelli N, Nocentini F, Baravelli S, et al. (1996) Endothelium and bone marrow transplantation. Bone marrow transplantation 17: 277–280.
31. Geraci JP, Mariano MS (1993) Radiation hepatology of the rat: parenchymal and nonparenchymal cell injury. Radiation research 136: 205–213.
32. Kowdley KV (2000) Ursodeoxycholic acid therapy in hepatobiliary disease. The American journal of medicine 108: 481–486.
33. Neuman MG, Shear NH, Bellentani S, Tiribelli C (1998) Role of cytokines in ethanol-induced cytotoxicity in vitro in Hep G2 cells. Gastroenterology 115: 157–166.
34. Lindner H, Holler E, Ertl B, Multhoff G, Schreglmann M, et al. (1997) Peripheral blood mononuclear cells induce programmed cell death in human endothelial cells and may prevent repair: role of cytokines. Blood 89: 1931–1938.
35. Rodrigues CM, Fan G, Ma X, Kren BT, Steer CJ (1998) A novel role for ursodeoxycholic acid in inhibiting apoptosis by modulating mitochondrial membrane perturbation. The Journal of clinical investigation 101: 2790–2799.
36. Pascolo L, Cupelli F, Anelli PL, Lorusso V, Visigalli M, et al. (1999) Molecular mechanisms for the hepatic uptake of magnetic resonance imaging contrast agents. Biochemical and biophysical research communications 257: 746–752.
37. Schuhmann-Giampieri G, Schmitt-Willich H, Press WR, Negishi C, Weinmann HJ, et al. (1992) Preclinical evaluation of Gd-EOB-DTPA as a contrast agent in MR imaging of the hepatobiliary system. Radiology 183: 59–64.
38. Watanabe H, Kanematsu M, Goshima S, Kondo H, Onozuka M, et al. (2011) Staging hepatic fibrosis: comparison of gadoxetate disodium-enhanced and diffusion-weighted MR imaging–preliminary observations. Radiology 259: 142–150.
39. Shin NY, Kim MJ, Lim JS, Park MS, Chung YE, et al. (2012) Accuracy of gadoxetic acid-enhanced magnetic resonance imaging for the diagnosis of sinusoidal obstruction syndrome in patients with chemotherapy-treated colorectal liver metastases. European radiology 22: 864–871.

Veröffentlichung 6

Radioablation of liver malignancies with interstitial high-dose-rate brachytherapy : Complications and risk factors.

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ORIGINAL ARTICLE

Radioablation of liver malignancies with interstitial high-dose-rate brachytherapy

Complications and risk factors

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Abstract
Background To evaluate complications and identify risk factors for adverse events in patients undergoing high-dose-rate interstitial brachytherapy (iBT).
Material and methods Data from 192 patients treated in 343 CT- or MRI-guided interventions from 2006–2009 at our institution were analyzed. In 41%, the largest tumor treated was ≥5 cm, 6% of the patients had tumors ≥10 cm. Prior to iBT, 60% of the patients had chemotherapy, 22% liver resection, 19% thermoablation or transarterial chemoembolization (TACE). Safety was the primary endpoint; survival data were obtained as the secondary endpoints. During follow-up, MRI or CT imaging was performed and clinical and laboratory parameters were obtained.
Results The rate of major complications was below 5%. Five major bleedings (1.5%) occurred. The frequency of severe bleeding was significantly higher in patients with advanced liver cirrhosis. One patient developed signs of a nonclassic radiation-induced liver disease. In 3 patients, symptomatic gastrointestinal (GI) ulcers were detected. A dose exposure to the GI wall above 14 Gy/ml was a reliable threshold to predict ulcer formation. A combination of C-reactive protein ≥165 mg/l and/or leukocyte count ≥12.7 Gpt/l on the second day after the intervention predicted infection (sensitivity 90.0%; specificity 92.8%.) Two patients (0.6%) died within 30 days. Median overall survival after the first liver treatment was 20.1 months for all patients and the local recurrence-free surviving proportion was 89% after 12 months.
Conclusions Image-guided iBT yields a low rate of major complications and is effective.

Keywords Liver neoplasms · Treatment efficacy · Local ablation · Hepatocellular carcinoma · Adverse events

Radioablation von Lebermalignomen mit interstitieller High-dose-rate-Brachytherapie

Komplikationen und Risikofaktoren

Zusammenfassung
Hintergrund Evaluierung der Komplikationsrate und Identifizierung von Risikofaktoren für Komplikationen und Nebenwirkungen bei Patienten mit Lebermalignomen, die mit der hochdosierten interstitiellen Brachytherapie (iBT) behandelt wurden.
Material und Methoden Von 2006 bis 2009 wurden 192 Patienten in 343 CT- oder MRT-geführten Interventionen behandelt und deren Daten ausgewertet. Der größte behandelte Tumor war in 41% der Fälle ≥5 cm, 6% der Patienten hatten Tumoren ≥10 cm. Vor Behandlungsbeginn hatten 60% der Patienten eine Chemotherapie, 22% eine Leberesektion und 19% eine Thermoablation oder transarterielle Chemoembolisation (TACE). Primärer Endpunkt war die Behandlungssicherheit, als sekundäre Endpunkte wurden Überlebensdaten ausgewertet. Die Nachsorge umfasste ne-

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ben klinischen und paraklinischen Parametern MRT- und CT-Untersuchungen.
Ergebnisse Die Rate an Major-Komplikationen lag unter 5%. Es traten 5 behandlungsbedürftige Blutungen auf (1,5%). Die Häufigkeit schwerer Blutungen war bei Patienten mit Leberzirrhose im fortgeschrittenen Stadium signifikant höher. Ein Patient entwickelte Zeichen einer nichtklassischen Strahlenhepatitis. Bei 3 Patienten zeigten sich symptomatische Magen-Darm-Ulzera. Eine Dosisexposition der Magen- bzw. Duodenalschleimhaut von mehr als 14 Gy/ml Einzeitdosis war mit dem Risiko von radiogen bedingten Ulzera verbunden. Eine CRP-Erhöhung auf mehr als ≥165 mg/l und/oder ein Anstieg der Leukozytenzahl auf mehr als ≥12,7 Gpt/l am 2. postinterventionellen Tag wies auf eine Infektion hin (Sensitivität 90,0%; Spezifität 92,8%). Die 30-Tage-Mortalität betrug 0,6%. Das mediane Gesamtüberleben nach der ersten Leberbehandlung betrug 20,1 Monate, die Lokalrezidivfreiheit nach 12 Monaten lag bei 89%.
Schlussfolgerung Die bildgeführte iBT hat eine niedrige Komplikationsrate und ist effektiv.

Schlüsselwörter Leberneoplasien · Behandlungswirksamkeit · Lokale Ablation · Hepatozelluläres Karzinom · Nebenwirkungen

Introduction

The diagnosis and treatment of primary and secondary liver malignancies have recently improved [1, 2]. Liver transplantation and surgical resection in patients with hepatocellular carcinoma (HCC) can potentially lead to cure in the minority of patients for whom these options are feasible [3]. In patients with small colorectal liver metastases (CRLM), 5-year survival rates between 7 and 58% are achieved [4, 5]. However, fewer than 25% of patients with CRLM are candidates for a potential curative treatment [6].

Thermoablative techniques have evolved for more than a decade; particularly, radiofrequency ablation (RFA) yields promising rates of tumor control and survival in small tumors [7–9]. However, RFA is of limited value in tumor lesions exceeding 3 cm in diameter, located close to the hepatic hilum or close to large vessels [10].

Precise radiotherapeutic techniques like stereotactic body radiotherapy (SBRT) has proven excellent local control, also after single-dose irradiation of liver tumors [11].

There is also experience with proton beam therapy, especially from Japan [12, 13]. Nonetheless, SBRT has demonstrated limitations in previous studies, such as a limited number of reasonably treatable metastases or a safe lesion diameter up to 4–5 cm [14, 15]. Beyond that size threshold, local tumor control rates after SBRT tend to decrease significantly [16, 17]. This has prompted the use of percutaneous image-guided interstitial high-dose-rate brachytherapy (iBT) [18]. Local control rates of up to 90% after 12 months and a prognostic impact in advanced and even very large HCC and CRLM have been found with a median overall survival (OS) of 19.4 and 23.4 months, respectively [19–21].

In liver malignancies of other primaries and in very large tumors, iBT has also been proven to be effective [22–26].

As iBT in the liver is an invasive procedure with an inhomogeneous dose distribution in contrast to percutaneous radiotherapy, and radiation is the tumor cell killing agent in contrast to conventional minimally invasive radiological techniques like radiofrequency ablation, a specific "complications spectrum" can be assumed with an exclusive impact on clinical practice. Therefore, its specific interventional and radiotherapeutic complication rate in a large patient cohort was the major goal of this study. To our knowledge, this is the largest study which thoroughly evaluates complications and risk factors for adverse events in patients with liver neoplasms treated with iBT.

Materials and methods

Study design

Patients treated at our institution with iBT from March 2006 to December 2007 were included in this study (group A, $N=144$). Treatment and safety data were documented prospectively in a dedicated database tailored to record treatment data and acute and chronic adverse events for later analysis. The frequency and quality of adverse events served as the primary endpoint. To address somatic discomfort more specifically, a second cohort of patients was recruited from December 2008 to March 2009 (group B, $N=48$) based on the same inclusion criteria, more closely monitored especially during the hospital stay with structured interviews to cover minor and more subjective side effects like mild pain and nausea more precisely.

Prior interventional therapies (e.g., RFA) were to have been completed at least 4 weeks before iBT; prior iBT had to be completed 3 months and yttrium90 radioembolization 6 months before iBT. Principal preconditions were a Child–Pugh score ≤8 points, a platelet count above 50 Gpt/l, and a prothrombin time of at least 50%. Ascites was not an exclusion criterion if controlled or minimal.

In general, we set a limit of liver involvement in a single session of not more than 5 Gy in two-thirds of the liver volume. In rare cases in patients with excellent liver function, this limit was exceeded.

Every 3 months, MRI or CT imaging was performed. Overall, progression-free and local recurrence-free survival

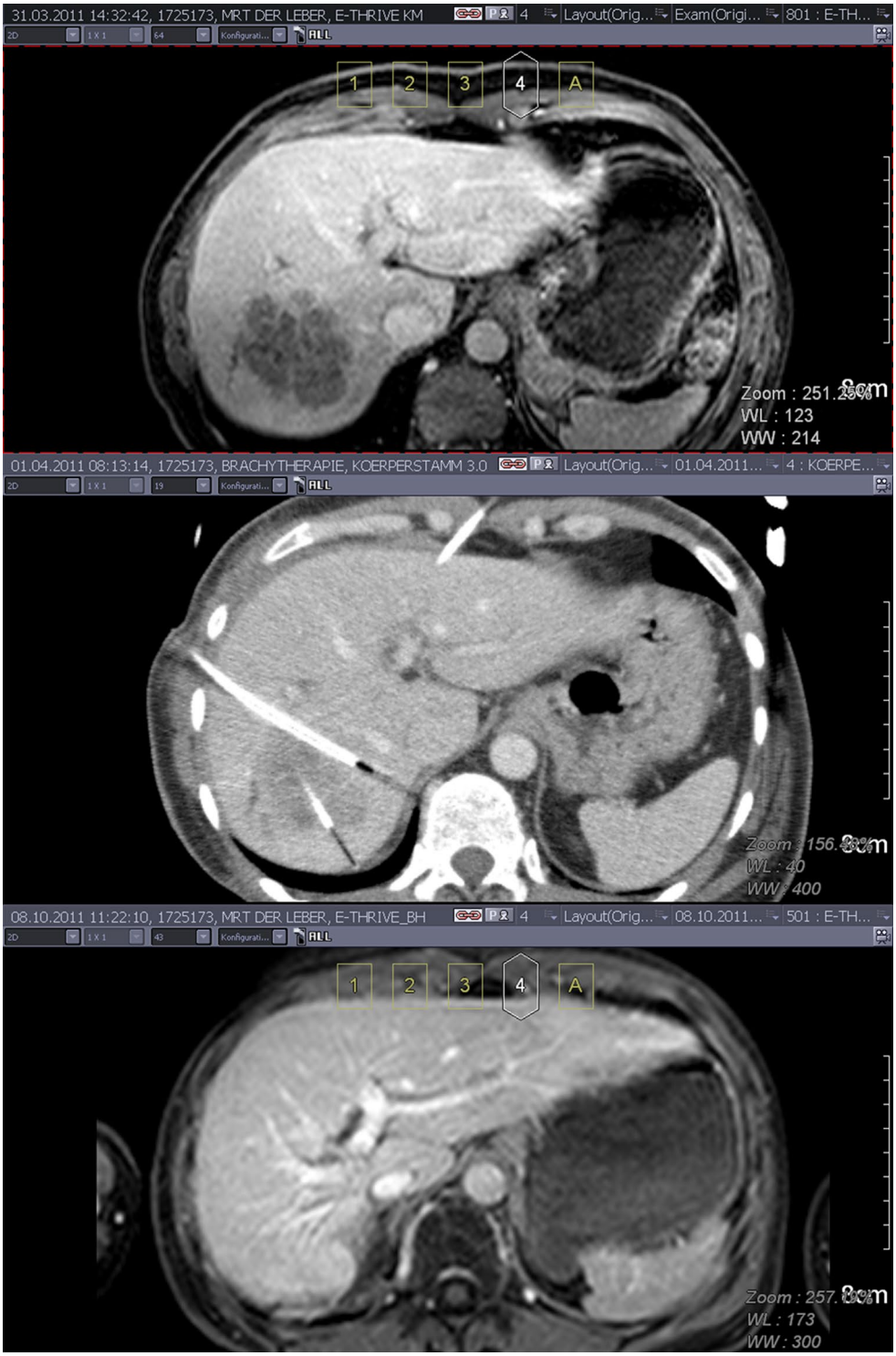

Fig. 1 A 42-year-old woman with breast cancer and hepatic metastasis. *Top* Pretherapeutic contrast-enhanced MRI. *Middle*: Contrast-enhanced CT after fluoroscopy-guided insertion of the iBT applicators. *Bottom* Contrast-enhanced MRI 6 months after iBT

were secondary endpoints. All patients provided written informed consent, and the study was approved by the local ethics committee.

Data acquisition

Postprocedural imaging was performed within the first 3 days. All patients treated at our institution were monitored closely with clinical examinations, laboratory, and CT or MRI imaging 6 and 12 weeks and then every 3 months for signs of adverse events or tumor progression (Fig. 1). Every

follow-up visit took place in our institution and the respective findings were documented in the mentioned database. In patient cohort A, this documentation was supplemented by thorough chart reviews, external documents, and telephone interviews (if events in the follow-up required such), whereas patient cohort B was additionally more closely monitored especially during the hospital stay with structured interviews to cover side effects regarding somatic discomfort such as pain and nausea more precisely.

Intervention and irradiation technique

Irradiation by the iBT technique, using an afterloading 10Ci iridium192 source system (Nucletron, the Netherlands) was performed. Positioning of the brachytherapy catheters was accomplished percutaneously either by fluoroscopy CT (Fig. 1, Toshiba Aquilion, Tokyo, Japan) or by real-time MRI (Panorama 1.0 T open MR system, Philips Healthcare) under a mild analgosedation, usually with midazolam and fentanyl. The catheter position, the tumor margin, and anatomic risk structures were verified by contrast-enhanced images sent to the treatment planning unit (Fig. 2 and 3, Oncetra-MasterPlan, Nucletron, the Netherlands; treatment characteristics: Tab. 1).

The target was defined as the gross tumor volume (GTV) on CT or MRI adding a safety margin of 2–3 mm in axial and craniocaudal directions. The prescribed dose at the tumor margin depended on the primary tumor based on findings from previous trials (e.g., hepatocellular carcinoma 15 Gy, and colorectal carcinoma 20 Gy) [20, 21]. Inhomogeneity of dose distribution was accepted with dose peaks in centrally located tumor regions, assumed that the prescribed dose at the tumor margin was reached.

Tab. 1 Interventional/radiotherapeutic characteristics and follow-up ($N=343$ interventions)

Variable	Value	Available data, *n* (%)
Guiding imaging		343 (100)
CT [*n* (%)]	284 (82.8)	
MRI [*n* (%)]	59 (17.2)	
Number of catheters [*n* (IQR; maximum)]	4.0 (2.0–5.0; 9)	342 (99.7)
Target dose per lesion [in Gy (±SD)]	17.3 (±3.1)	337 (98.3)
CTV [in cm^3 (IQR; maximum)]	36.7 (13.0–78.8; 796.0)	317 (92.4)
LV [in cm^3 (±SD)]	1352.3 (±413.5)	295 (86.0)
(CTV/LV) × 100 [% (IQR; maximum)]	2.7 (1.1–6.1; 61.2)	291 (84.8)
(5 Gy/LV) × 100[a] [% (IQR; maximum)]	22.5 (13.8–34.7; 87.9)	293 (85.4)

CTV clinical target volume, *LV* liver volume, *IQR* interquartile range, *SD* standard deviation.

[a]5 Gy-volume of total tumor-free liver volume.

Attendance for follow-up was as follows: nominally 3 days (actually 2.9±0.9 days, appointments kept by patients representing 343/343 interventions); 6 weeks (42±12 days, appointments kept by patients representing 269/288 interventions); 3 months (85±12 days, 139/196); 6 months (147±29 days, 113/144); 9 months (215±34 days, 85/106); 12 months (293±33 days, 56/60); 15 months (386±39 days, 42/45); 18 months (484±41 days, 37/37); 21 months (611±49 days, 20/20); 24 months (712±58 days, 9/9)

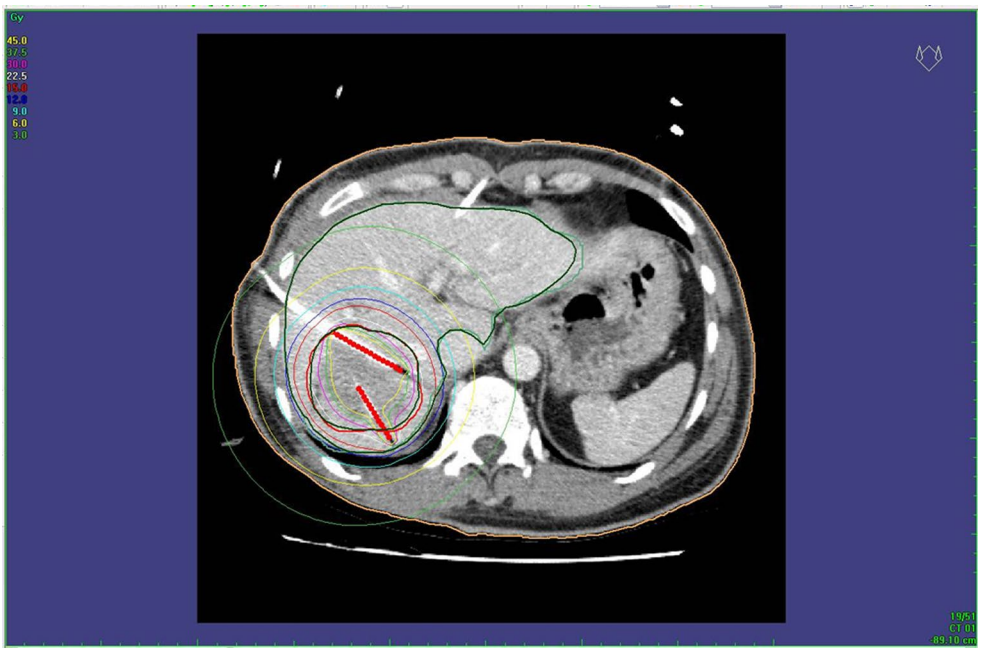

Fig. 2 iBT planning based on interventional contrast-enhanced CT

Analysis and statistical methods

Adverse events were graded according to the 3rd version of the National Cancer Institute's Common Terminology Criteria for Adverse Events [27]. Furthermore, liver function was assessed according to the criteria for radiation-induced liver disease (RILD) [28]. Time to progression (TTP) and overall survival (OS) were estimated by the Kaplan–Meier method and compared by employing the log-rank, Breslow, and Tarone–Ware tests. Calculations were performed with SPSS® software, version 15 (SPSS Inc., Chicago, IL, USA).

Results

Patients and procedures

A total of 192 patients with primary and secondary malignancies of the liver were treated in 343 interventions, in which 1275 brachytherapy catheters were placed [patients with colorectal liver metastases (LM), $n=84$; hepatocellular carcinoma, $n=50$; cholangiocellular carcinoma, $n=16$; breast cancer LM, $n=13$; lung cancer LM, $n=8$; and 21 patients with LM of other origin]. The average clinical target volume (CTV) was 36.7 ml [interquartile range (IQR) 13–78.8 ml]. The mean number of lesions treated per patient was 1.5 (range 1–5).

Of 296 lesions, 277 were treated in a single session (median 16.4 Gy, range 5.9–31.2 Gy). The corresponding median biologically effective dose (BED) was 43.3 (range 9.4–128.5); the equivalent dose in 2 Gy fractions (EQD2) was 36.1 (range 7.8-107.1).

A total of 19 large to very large lesions were treated in 2 or 3 sessions dividing the tumor in different CTV for each single session (median 2 fractions, range 2–3, e.g., upper part and lower part). The median dose/fraction was 10.0 Gy (range 3.5–15.9 Gy). The corresponding median total BED was 50.3 (range 31.4–141.4), the EQD2 was 41.9 (range 26.1–117.8). If new lesions were treated with iBT during follow-up and the inclusion criteria were met, these interventions were included in the analysis. The proportion of the total liver volume exposed to at least 5 Gy (V5) in a single irradiation session was 22.5% on average (max. 88%). Treatment decisions were based on interdisciplinary consensus. Detailed information regarding tumor treatment are shown in Table 1 and baseline characteristics of the study population are shown in Table 2. Of the 192 patients, 111 received more than one iBT.

Complications

Overall, the proportion of patients with major complications was below 5% (15/343). Full details are given in Table 3.

Tab. 2 Baseline patient characteristics. ($N=192$ patients; number of patients (%) are shown except where otherwise stated)

Age, years (mean ± SD)	66.08 (± 10.2)
Male	111 (57.8)
Tumor entity	
Colorectal carcinoma	84 (43.8)
Hepatocellular carcinoma	50 (26.0)
Cholangio carcinoma	16 (8.3)
Mammary carcinoma	13 (6.7)
Lung carcinoma	8 (4.2)
Others[a]	21(10.9)
Diameter of the largest lesion	
< 5 cm	105 (54.7)
5-–10 cm	66 (34.4)
> 10 cm	12 (6.3)
Diffuse tumor spread	9 (4.7)
More than one lesion to treat	79 (41.1)
Previous chemotherapy	114 (59.4)
First line	38 (33.3)
Second line or more	76 (66.7)
Previous liver resection	52 (22.4)
Previous tumor ablation[b]	51 (26.6)
RFA or LITT	23 (45.1)
TACE	13 (25.5)
iBT	15 (29.4)
Stereotactic radiation	1 (2.0)
Previous other therapies[c]	12 (6.3)
Liver cirrhosis	50 (26.0)
Child–Pugh class A (76 interventions)	44 (88.0)
B (12 interventions)	6 (12.0)
Portal vein thrombosis (30 interventions)[d]	15 (7.8)
Karnofsky index ≥ 70%	188 (97.9)

[a]Leiomyosarcoma of the vena cava, urinary bladder cancer, gastric cancer, renal cell cancer, jejunal cancer, adenocarcinoma of unknown primary (2 each) and esophageal cancer, pancreatic cancer, gastrointestinal stroma tumor, cervical cancer, thyroid cancer, anal cancer, hypopharyngeal cancer, choroidal melanoma, prostate cancer (1 each).

[b]*RFA* radiofrequency ablation, *LITT* Laser Induced Thermo Therapy, *TACE* transarterial chemoembolization, *iBT* interstitial HDR brachytherapy.

[c]Additional hormone or tyrosine-kinase inhibitor therapy.

[d]Thrombosis in the main, right or left hemiliver portal vein.

Bleeding CTCAE grade ≥ III

The mean preinterventional platelet count differed significantly between patients with and without postinterventional bleeding [160.0 Gpt/l (range 87.5–256.0 Gpt/l) vs. 244.3 Gpt/l (range 165.0–303.3 Gpt/l); $p=0.043$], but not for age, the number of catheters placed [5.0 (range 2.5–6.0) vs. 4.0 (2.0–5.0); $p=0.410$], the incidence of portal vein thrombosis (20.0 vs. 9.4%; $p=0.390$), and the preinterventional prothrombin time. Major bleeding occurred exclusively in patients with liver cirrhosis (5/89 'with' vs. 0/254

Tab. 3 Complications after iBT and subsequent treatments

Complication	Cases, *n* (%)[a]	Therapy[b]	Interval[c]
Major			
Bleeding CTCAE IV	1 (0.29)	Surgery, resolved	24 h
Bleeding CTCAE III	4 (1.17)	DSA and/or PRBC, resolved	24 h
Ascites CTCAE III	1 (0.29)[e]	Drainage and diuretics, resolved	48 h
Ulcer, GI	3 (0.87)	Endoscopic intervention, resolved	5 weeks–8 months
Non-classic RILD	1 (0.5)[h]	Symptomatic, UDC, resolved	7 weeks
Liver abscess	4 (1.17)[g]	Drainage and antibiotics, resolved	4 days–8 months
Bile duct occlusion[d]	1 (0.29)	Endoscopic stenting, resolved	1 week
30-day mortality	2 (1.0)[h]		
Minor			
Bleeding CTCAE I	9 (3.21)	None, resolved	24 h
Pleural effusion CTCAE I	31 (10.8)	None, resolved	24–72 h
Pleural effusion CTCAE II	4 (1.40)[f]	Thoracentesis, resolved	24–72 h
Pneumothorax CTCAE I	4 (1.40)	None, resolved	24 h
Pneumothorax CTCAE II	1 (0.35)	Chest tube, resolved	24 h
Ascites CTCAE I	2 (0.71)	None, resolved	24–72 h

iBT interstitial brachytherapy, *DSA* digital subtraction angiography with embolization, *PBRC* packed red blood cells, *CTCAE* Common Terminology Criteria for Adverse Events, *GI* gastrointestinal, *UDC* ursodeoxycholic acid, *RILD* radiation-induced liver disease.

[a]Percentages for major complications: based on total of 343 iBT procedures; for minor complications: based on the number of imagings performed 3 days after intervention (abdomen: 280, chest: 286).

[b]Therapy to treat given event.

[c]Usual time after iBT that event was observed. Some cases of hematoma/hemorrhage, pneumothorax occurred during the procedure.

[d]Edema related occlusion of a central bile tract.

[e]Increased from preinterventional grade I.

[f]Two increased from preinterventional grade I.

[g]One abscess was related to percutaneous transhepatic cholangio drainage.

[h]Percentage: patient-based.

'without'; $p=0.001$). In particular, the incidence was much higher in patients with severe liver dysfunction ['Child B/C' 3/13 vs. 'no cirrhosis or Child A': 2/330, with odds ratio (OR) 49.20 and 95% confidence interval (CI) 7.38–327.83; $p<0.001$].

Gastrointestinal ulcers

Seventy-two interventions in 57 patients were associated with exposure of the upper GI tract to >1 Gy in the cubic centimeter subjected to the greatest exposure. Three symptomatic postinterventional GI ulcers occurred in the gastric wall, the duodenal wall and the gastroduodenal junction, respectively (3/72; 4.2%). Interventions associated with GI ulcers showed a higher minimum dose applied to 1 ml (D_{1CC}) of the GI mucosa than interventions without ulcers (15.8±2.5 vs. 10.0±4.1 Gy; $p=0.020$). A dose exposure of the GI wall above 14 Gy was a reliable threshold to predict postinterventional ulcer formation (3/15 vs. 0/57, $p=0.008$) and this dose was less frequently (and not significantly) associated with ulcer formation when the patient received mucosal protection by the intake of a proton pump inhibitor (PPI; 2/5 [40%] vs. 1/10 [10%]; $p=0.242$).

Liver function

Transient elevation of bilirubin and liver enzymes without a clinically relevant impact was frequent. No case of classic RILD was found. However, one patient suffered from liver dysfunction after several treatments without any evidence of hepatic tumor progression. That patient with a relapsed hepatocellular carcinoma 22 months after resection of the left liver lobe and hepatitis C with steatohepatitis and preprocedural preserved liver function (Child A) developed ascites and an icteric elevation of liver enzymes with a 5fold elevation of bilirubin, a >5fold elevation of alkaline phosphatase, and a 3fold elevation of transaminases 7 weeks after the last of four brachytherapy sessions. The close chronological link to repeated iBT, the underlying hepatitis C, and the subsequent course makes this likely to have been a case of nonclassic RILD. Under symptomatic and diuretic treatment and administration of ursodeoxycholic acid these values reverted to almost normal levels within 7 months. The patient died 27 months after the last brachytherapy.

Postinterventional infection

Overall, ten postprocedural infections (10/343, 2.92%), including four liver abscesses, were diagnosed. Further septic complications comprised of three cases of cholangitis and one of pneumonia. On the basis of clinical presentation, laboratory results, and response to antibiotic therapy, two infections without a specific focus were diagnosed. Eight infections were diagnosed after discharge from hospital.

Fever (>38 °C) occurred in approximately 10% of interventions but was not significantly associated with infection ($p=0.260$). Serum levels of postinterventional C-reactive protein (CRP) positively correlated with the clinical target volume (CTV; $r=0.473$; $p<0.001$; $n=312/343$). Patients

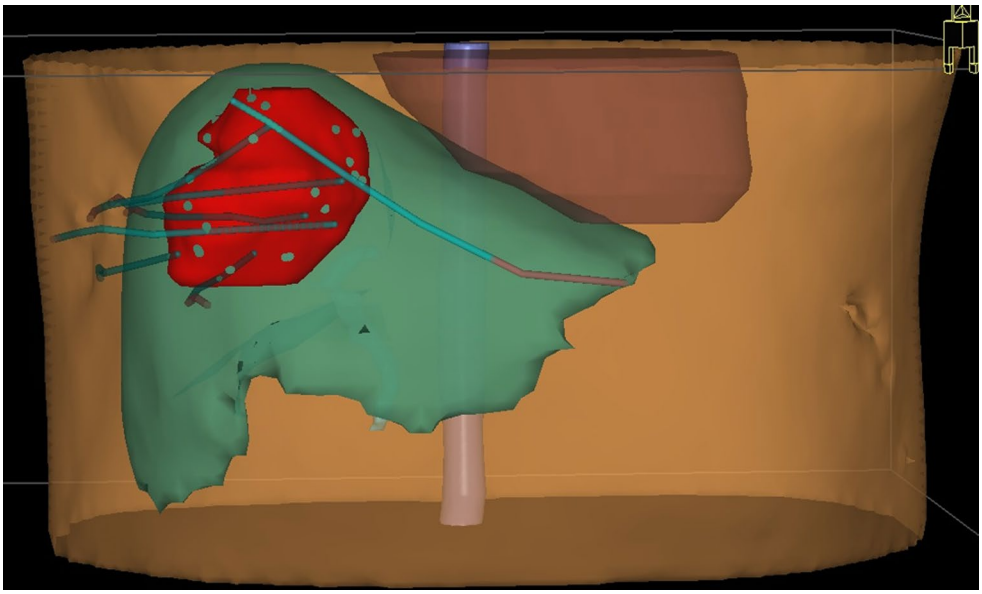

Fig. 3 The 3D tumor volume with the labeled catheter position

with postinterventional infection showed a higher level of CRP on the second postinterventional day than did patients without infection [129.8 mg/l (range 69.1–197.4) vs. 51.1 mg/l (range 24.1–90.6); $p<0.001$; $n=333/343$] and the mean leukocyte count was higher in these patients (12.8±4.1 Gpt/l vs. 7.4±2.9 Gpt/l; $p<0.001$, $n=337/343$). Univariate binary logistic regression analysis indicated that the postinterventional level of plasma leucocytes and the CRP (both on the second day) were predictive for septic events after iBT ($p<0.001$). In a binary regression analysis, prediction of postinterventional infection was even stronger when both variables were included ($p<0.001$).

Postinterventional CRP (2nd day after iBT) ≥165 mg/l *and/or* leukocyte count ≥12.7 Gpt/l revealed a sensitivity of 90.0% and a specificity of 92.8% for diagnosis of postprocedural infection.

30-day mortality

Two patients died within 30 days after a single brachytherapy not directly related to the intervention: One patient with Child–Pugh B liver cirrhosis died of severe esophageal bleeding 27 days after the procedure. Another patient died of neutropenic sepsis during chemotherapy after 29 days. This corresponded to 1.04% of all patients and 0.58% of all interventions.

Nausea/vomiting

Fifty-one events of nausea and/or vomiting were documented in 274 interventions (group A: 18.6%; vomiting: 19 grade I, 14 grade II; nausea: 35 grade I, 11 grade II). In group B ($n=69$), 26 (37%) were associated with nausea and/or vomiting (vomiting, 6 grade I and 10 grade II; nausea, 23 grade I and 2 grade II). In female patients, nausea and/or vomiting were more frequent (OR 2.89 with 95% CI 1.05–7.94; $p=0.049$).

Somatic discomfort

Severe pain (7/343, 2.0%) was associated with major bleeding or its management (3/5 vs. 4/338; $p<0.001$). In female patients, pain was more frequent (OR 3.53 with 95%CI 1.31–9.52; $p=0.016$).

Survival

Median follow-up time for survival was 20.5 months. Median OS after the first liver brachytherapy (not necessarily identical with the first intervention at our institution) for all patients was 20.1 months. Specifically, this was 27.9 months for breast cancer patients, 21.5 and 21.2 months for patients with colorectal liver metastases and hepatocellular carcinoma, 16.3 months for patients with cholangiocellular carcinoma, 8.7 months for lung cancer patients, and 24.1 months for patients with other malignancies. Eighty-three (43.2%) of patients also had extrahepatic disease [OS 22.3 (liver only) and 18.3 months (extrahepatic disease), respectively, $p<0.05$]. Median time to progression was 5.5 months, ranging from 11.7 months in patients with hepatocellular carcinoma to 2.2 months in patients with lung cancer.

Local recurrences (LR) were defined as any tumor growth, at any time point after iBT, adjacent to the field of administered radiation. Forty-four lesions (14.9%) of 296 treated developed a local recurrence (LR) with a 12-month local control rate (LCR) of 89% for all lesions (ranging from 97% in HCC lesions to 84% in colorectal liver metastases). A multivariate Cox regression including tumor diameter,

clinical target volume (CTV) and dose covering 100 % of the CTV (D100) revealed the significant influence of D100 upon LR-free survival only in colorectal liver metastases ($p = 0.03$), while this was not the case for lesions of other origin. Neither tumor diameter nor CTV had a significant effect on LR-free survival.

Discussion

Data from this study suggest that the safety of iBT compares to that of other minimally invasive ablation methods such as RFA. This is remarkable because iBT is predominantly conducted in patients unsuitable for RFA because of a high-risk location and/or the size of the lesion. The interventional major complication rate of 4.1 % in iBT is equivalent to that reported for RFA (4.1 %) and below the surgical complication rate [29, 30].

The greater complication rate in cirrhotic than in non-cirrhotic patients was also found in an earlier trial of iBT in HCC [19, 20]. Interestingly, beside cirrhosis no bleeding risk factors other than the platelet count were identified. This might also be due to catheter channel closing by gelaspone particles.

Streitparth et al. [31] showed in a small patient group that a dose exposure of the upper GI mucosa of 15.5 Gy (D1CC) was predictive of gastric ulceration after a single iBT. This finding is supported by our data, with a threshold of 14 Gy. Therefore, we now routinely start patients on PPI, when the dose exceeds 5 Gy to the highest exposed mucosal area.

The frequency of severe to irreversible liver toxicity is very low irrespective of single doses of up to 25 Gy, and of repetitive high-dose radiotherapies, as supported by findings of Ruehl et al. [32]. Only one patient (with diminished liver function and liver cirrhosis) developed reversible signs and symptoms of a nonclassic RILD after repetitive iBT (0.5 %). Bujold et al. [33] reported a rate of fatal liver failures of 5 % in patients receiving SBRT for HCC. In a trial of Kawashima et al. [34], 11 of 60 patients (18,3 %) with HCC treated with PBT developed a radiation-induced liver disease (RILD, or proton-induced hepatic insufficiency, PHI), of whom 7 patients (11 %) died of PHI. Two distinctive features might be responsible for the obvious high liver resistance to brachytherapeutic radiotherapy. First, the steep dose gradient results at least in a sharply defined and predictable scar, comparable to surgical tumor enucleation or atypical resection [35]. This also minimizes unnecessary exposure of the uninvolved parenchyma. Second, a part of the highly exposed liver parenchyma recovers over time [36, 37]. This is also in concordance with the findings of Brinkhaus et al. [38]. Facultative or obligate preventive medication to avoid RILD is established in ^{90}Y radioembolization, and a recent report by Seidensticker et al. has proven the effectiveness in iBT [39, 40].

A postinterventional (2nd day after iBT) CRP of ≥165 mg/l and/or leukocyte count ≥12.7 Gpt/l was considered to be a reliable threshold for distinguishing reactive elevations from inflammatory complications.

In this trial, 41 % of the lesions treated exceeded 5 cm in diameter but the 12 months local control rate ranged from 97 % in hepatocellular carcinoma to 84 % in colorectal liver metastases despite the fact that patients with limited disease were included, receiving a more or less “curative” intended high dose as well as patients with an advanced stage of disease with palliative treatment and lower doses.

Overall, our results indicate that iBT is a safe and effective procedure in heavily pretreated patients.

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Compliance with ethical standards

Conflict of interest K. Mohnike, S. Wolf, R. Damm, M. Seidensticker, R. Seidensticker, F. Fischbach, N. Peters, P. Hass, G. Gademann, M. Pech, and J. Ricke state that there are no conflicts of interest.

The study was conducted in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki and ICH-GCP. The study protocol and all study-related documentation were approved by all relevant authorities.

References

1. Deshpande R, O’Reilly D, Sherlock D (2011) Improving outcomes with surgical resection and other ablative therapies in HCC. Int J Hepatol 2011:686074
2. Pawlik TM, Assumpcao L, Vossen JA et al (2009) Trends in non-therapeutic laparotomy rates in patients undergoing surgical therapy for hepatic colorectal metastases. Ann Surg Oncol 16:371–378
3. Dhir M, Lyden ER, Smith LM, Are C (2012) Comparison of outcomes of transplantation and resection in patients with early hepatocellular carcinoma: a meta-analysis. HPB (Oxford) 14:635–645
4. Jones RP, Jackson R, Dunne DF et al (2012) Systematic review and meta-analysis of follow-up after hepatectomy for colorectal liver metastases. Br J Surg 99:477–486
5. Smith MD, McCall JL (2009) Systematic review of tumour number and outcome after radical treatment of colorectal liver metastases. Br J Surg 96:1101–1113
6. Khatri VP, Petrelli NJ, Belghiti J (2005) Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? J Clin Oncol 23:8490–8499
7. Cirocchi R, Trastulli S, Boselli C et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. Cochrane Database Syst Rev 6:CD006317
8. Ruers T, Punt C, Van Coevorden F et al (2012) Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 23:2619–2626

9. Sutherland LM, Williams JA, Padbury RT, Gotley DC, Stokes B, Maddern GJ (2006) Radiofrequency ablation of liver tumors: a systematic review. Arch Surg 141:181–190
10. Tanis E, Nordlinger B, Mauer M et al (2014) Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983. Eur J Cancer 50:912–919
11. Herfarth KK, Debus J, Lohr F et al (2001) Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. J Clin Oncol 19:164–170
12. Bush DA, Kayali Z, Grove R, Slater JD (2011) The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: a phase 2 prospective trial. Cancer 117:3053–3059
13. Kawashima M, Furuse J, Nishio T et al (2005) Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. J Clin Oncol 23:1839–1846
14. Dawson LA (2011) Overview: where does radiation therapy fit in the spectrum of liver cancer local-regional therapies? Semin Radiat Oncol 21:241–246
15. Scorsetti M, Arcangeli S, Tozzi A et al. Is stereotactic body radiation therapy an attractive option for unresectable liver metastases? A preliminary report from a phase 2 trial. Int J Radiat Oncol Biol Phys 2013;86:336–342
16. Dawood O, Mahadevan A, Goodman KA (2009) Stereotactic body radiation therapy for liver metastases. Eur J Cancer 45:2947–2959
17. Kirkpatrick JP, Kelsey CR, Palta M et al (2014) Stereotactic body radiotherapy: a critical review for nonradiation oncologists. Cancer 120:942–954
18. Ricke J, Wust P, Wieners G et al (2004) Liver malignancies: CT-guided interstitial brachytherapy in patients with unfavorable lesions for thermal ablation. J Vasc Interv Radiol 15:1279–1286
19. Mohnike K, Wieners G, Pech M et al (2009) Image-guided interstitial high-dose-rate brachytherapy in hepatocellular carcinoma. Dig Dis 27:170–174
20. Mohnike K, Wieners G, Schwartz F et al. (2010) Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: safety, efficacy, and effect on survival. Int J Radiat Oncol Biol Phys 78:172–179
21. Ricke J, Mohnike K, Pech M et al. (2010) Local response and impact on survival after local ablation of liver metastases from colorectal carcinoma by computed tomography-guided high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 78:479–485
22. Collettini F, Poellinger A, Schnapauff D et al (2011) CT-guided high-dose-rate brachytherapy of metachronous ovarian cancer metastasis to the liver: initial experience. Anticancer Res 31:2597–2602
23. Collettini F, Schnapauff D, Poellinger A et al (2012) Hepatocellular carcinoma: computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of large (5–7 cm) and very large (> 7 cm) tumours. Eur Radiol 22:1101–1109
24. Tselis N, Chatzikonstantinou G, Kolotas C, Milickovic N, Baltas D, Zamboglou N (2013) Computed tomography-guided interstitial high dose rate brachytherapy for centrally located liver tumours: a single institution study. Eur Radiol 23:2264–2270
25. Wieners G, Mohnike K, Peters N et al (2011) Treatment of hepatic metastases of breast cancer with CT-guided interstitial brachytherapy - a phase II-study. Radiother Oncol 100:314–319
26. Wieners G, Pech M, Hildebrandt B et al (2009) Phase II feasibility study on the combination of two different regional treatment approaches in patients with colorectal "liver-only" metastases: hepatic interstitial brachytherapy plus regional chemotherapy. Cardiovasc Intervent Radiol 32:937–945
27. Trotti A, Colevas AD, Setser A et al (2003) CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 13:176–181
28. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF (1995) Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 31:1237–1248
29. Bertot LC, Sato M, Tateishi R, Yoshida H, Koike K (2011) Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. Eur Radiol 21:2584–2596
30. Cheung TT, Poon RT, Yuen WK et al (2013) Long-term survival analysis of pure laparoscopic versus open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a single-center experience. Ann Surg 257:506–511
31. Streitparth F, Pech M, Bohmig M et al (2006) In vivo assessment of the gastric mucosal tolerance dose after single fraction, small volume irradiation of liver malignancies by computed tomography-guided, high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 65:1479–1486
32. Ruhl R, Seidensticker M, Peters N et al (2009) Hepatocellular carcinoma and liver cirrhosis: assessment of the liver function after Yttrium-90 radioembolization with resin microspheres or after CT-guided high-dose-rate brachytherapy. Dig Dis 27:189–199
33. Bujold A, Massey CA, Kim JJ et al (2013) Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 31:1631–1639
34. Kawashima M, Kohno R, Nakachi K et al (2011) Dose-volume histogram analysis of the safety of proton beam therapy for unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 79:1479–1486
35. Seidensticker M, Seidensticker R, Mohnike K et al (2011) Quantitative in vivo assessment of radiation injury of the liver using Gd-EOB-DTPA enhanced MRI: tolerance dose of small liver volumes. Radiat Oncol 6:40
36. Ricke J, Seidensticker M, Ludemann L et al (2005) In vivo assessment of the tolerance dose of small liver volumes after single-fraction HDR irradiation. Int J Radiat Oncol Biol Phys 62:776–784
37. Ruhl R, Ludemann L, Czarnecka A et al (2010) Radiobiological restrictions and tolerance doses of repeated single-fraction hdr-irradiation of intersecting small liver volumes for recurrent hepatic metastases. Radiat Oncol 5:44
38. Brinkhaus G, Lock JF, Malinowski M et al (2014) CT-guided high-dose-rate brachytherapy of liver tumours does not impair hepatic function and shows high overall safety and favourable survival rates. Ann Surg Oncol 21:4284–4292
39. Sangro B, Gil-Alzugaray B, Rodriguez J et al (2008) Liver disease induced by radioembolization of liver tumors: description and possible risk factors. Cancer 112:1538–1546
40. Seidensticker M, Seidensticker R, Damm R et al (2014) Prospective randomized trial of enoxaparin, pentoxifylline and ursodeoxycholic Acid for prevention of radiation-induced liver toxicity. PLoS One 9:e112731

Veröffentlichung 7

Y90 Radioembolization in chemo-refractory metastastic, liver dominant colorectal cancer patients: outcome assessment applying a predictive scoring system.

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RESEARCH ARTICLE Open Access

Y90 Radioembolization in chemo-refractory metastastic, liver dominant colorectal cancer patients: outcome assessment applying a predictive scoring system

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Abstract

Background: In treatment-refractory liver dominant metastatic colorectal cancer, the role of liver directed therapies still is unclear. We sought to determine a prognostic score for Y90 radioembolization in these patients.

Methods: We analyzed 106 patients with refractory liver dominant mCRC who had undergone a total of 178 Y90 radioembolizations with resin microspheres was collected. Potential factors influencing survival were analyzed using a Cox regression. The Log rank test served to establish prognostic factors and to form a clinical score for outcome prediction after Y90 radioembolization.

Results: Median survival of all patients was 6.7 months. Neither age nor prior surgical or systemic therapy nor metastatic spread had an effect on survival. In contrast, hepatic tumor load, Karnofsky index as well as CEA and CA19-9 serums level had a significant influence ($p < 0.001$, $p = 0.037$, $p = 0.023$ and $p < 0.001$, respectively). These three factors formed a score with 1 point each for tumor load >20 %, CEA >130 ng/ml or CA19-9 > 200U/ml and Karnofsky index <80 %. Patients with a score of 0 and 1 displayed a median OS of 10.4 months. Patients with a score of 2 and 3 demonstrated a median OS of 5.1 months only ($p < 0.001$).

Conclusion: Overaggressive patient selection for Y90 radioembolization of liver dominant chemorefractory mCRC is of questionable benefit. A scoring system comprising hepatic tumor load, CEA and CA19-9 serum levels and Karnofsky index (TuCK-score) may support an improved patient selection. In our cohort of liver only versus liver dominant disease, extrahepatic lung or lymphatic metastases did not significantly alter the prognosis.

Keywords: Y90 radioembolization, Colorectal cancer, Liver metastases, Salvage patients, Prognostic score

Background

In treatment-refractory liver dominant metastatic colorectal cancer, the role of liver directed therapies still is unclear. For Yttrium 90 (Y90) radioembolization (RE), objective response rates between 33 and 48 % have been published when applied in second line [1, 2], and between 10 and 48 % in third line [3–6]. In a refractory third line setting Seidensticker et al. reported improved survival in a match pair study of 3.5 vs 8.3 months[6]. Hendlisz et al. randomized between 5-fluorouracil (5-FU) +/− Y90 radioembolization in refractory third line patients and demonstrated a survival benefit of 10 versus 7.3 months, as well as a significant progression free survival (PFS) improvement of 4.3 vs 2.1 months. The latter study led to inclusion of Y90 radioembolization in the ESMO guidelines for colorectal cancer, however with a low strength of recommendation (IV, B) [7].

In clinical practice, treatment recommendations for refractory patients are challenging. Many patients present with advanced tumor load in a biologically unfavorable state of disease progression, potentially aggravated by

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comorbidities and a poor performance status. Palliation in such patients must balance the patient´s desire for life prolongation and an acceptable quality of life to withstand the hazards of aggressive treatments. Hence, a careful patient selection is of utmost importance. For Y90 radioembolization, no adequate predictive factors have been published in treatment refractory colorectal cancer patients yet, baring the risk of overtreatment as a result of inappropriate patient selection.

In the study described herein we analyzed a cohort of 106 patients with chemo-refractory, liver dominant colorectal cancer undergoing Y90 radioembolization at our institution. We sought to determine predictive factors to aid a responsible patient selection balancing the potential survival benefits against the inadvertent risk of an aggressive liver directed therapy.

Methods

Study design and eligibility criteria

Our patient database was reviewed for patients with colorectal cancer liver metastases undergoing Y90-radioembolization in our department between 2006 and 2010. We collected retrospective data on prior surgical or systemic treatments, disease spread, clinical performance, tumor markers and survival. All patients had been scheduled for routine follow-up every 3 months at our department including a documentation of their clinical performance, disease response in Computed tomography (CT)/magnetic resonance imaging (MRI) and laboratory values. We selected all patients who met the following criteria:

- liver metastases of colorectal carcinoma,
- admitted and eligible for Y90-radioembolization,
- salvage situation (either refractory to all accepted chemotherapy regimen at the time of admission or refusal of or non-eligibility to further systemic therapies after at least one cycle).

Patient cohort

We included a total of 106 salvage patients with liver metastases from colorectal cancer (70 male, 36 female; mean age 61.9 years). All patients had failed at least one chemotherapy regimen; the median number of chemotherapy lines applied was 3. 26 % of the patients had failed four or more lines of systemic therapy. About half of the patients had received bevacizumab ($n = 67$) and/or cetuximab ($n = 51$) prior to radioembolization. 27 presented under maintenance therapy with capecitabine. Other cytotoxic regimen such as a combination of mitomycin and 5-FU were applied to 7 patients before admittance to Y90 radioembolization.

In 22 patients, a contraindication such as bone marrow depression or unwillingness to receive further chemotherapies (mostly as a result of previous toxicity such as polyneuropathy) led to discontinuation of systemic therapies.

Thirty patients had previously undergone hepatic resection or radiofrequency ablation before Y90 radioembolization. Whereas 86 patients presented liver only disease, 30 patients demonstrated extrahepatic tumor spread such as lymph node metastases ($n = 17$), lung metastases ($n = 16$, with 15 patients displaying more than one pulmonary metastases) and bone metastases ($n = 4$). Further details of patient characteristics are displayed in Table 1.

Clinical evaluation and radioembolization technique

All patients underwent a thorough clinical examination prior to radioembolization including a physical examination, laboratory tests and cross-sectional imaging including MRI with hepatocyte-specific contrast agent Gd-EOB-DTPA (Primovist®, Bayer HealthCare, Leverkusen, Germany).

The technique of Y90 radioembolization has been described in detailed elsewhere [8].

All patient scheduled for radioembolization received an initial evaluation angiography. The work up included coil or plug embolization of visceral collaterals if appropriate. After the test infusion of Technecium-99 m macro-aggregated albumin (Tc-99 m MAA, LyoMAA, Covidien, Neustadt, Germany) to the liver arteries, a scintigraphy including a SPECT-CT was performed to rule out extrahepatic accumulation or inadvertent lung shunting. In the latter case, a lung shunt above 10 % led to a dose reduction as specified by the summary of product characteristics. Dosimetry was performed applying the body-surface area model [9].

Liver metastases were treated exclusively employing resin microspheres (SIR-Spheres®, Sirtex Medical, Lane Cove, Australia) labeled with beta-emitter Yttrium-90 (half-life 64 h; mean energy 0.96 MeV). The catheter position during Y90 application was identical to the test bolus of Tc-99 m MAA during the evaluation. Starting in 2007, radioembolization was typically partitioned in sequential therapies for each liver lobe at an interval of 4 to 6 weeks. In patients presenting with disease limited to one liver lobe, Y90 spheres were applied in the according lobe only with a dose calculation adopted to the reduced liver volume [10]. Before 2007, we exclusively performed whole liver treatments.

All patients gave written informed consent to both radioembolization as well as the scientific use of their personal data. The institutional ethics committee deemed a dedicated ethics vote unnecessary for the present analysis. This scientific paper has been written according to the reporting standards for radioembolization [11].

Table 1 Patient characteristics

Patient characteristics		
Female	*n* = 36	33,9 %
Male	*n* = 70	66,1 %
Age (median (range), years)	62.5 (33.0 -76.0)	
Karnofsky index (median (range), %)	80 (60–100)	
Pretreatment characteristics		
Prior resection or radiofrequency ablation	*n* = 30	28 %
Prior chemotherapy agents		
Oxaliplatin (+5-fluorouracil)	*n* = 79	75 %
Irinotecan (+5-fluorouracil)	*n* = 89	84 %
Capecitabine	*n* = 27	25 %
Bevacizumab	*n* = 67	63 %
Cetuximab	*n* = 51	48 %
Other	*n* = 7	7 %
Overall chemotherapy lines (median (range))	3 (1–5)	
1st Line	*n* = 9	8 %
2nd Line	*n* = 35	33 %
3rd Line	*n* = 34	32 %
4th Line and beyond	*n* = 28	26 %
Tumor characteristics		
UICC stage (median (range))	4 (1–4)	
Grading (median (range))	2 (1–4)	
Synchronous lymphatic metastases	*n* = 80	75 %
Extrahepatic tumor sites prior to radioembolization	*n* = 30	28 %
Solitary/oligonodular lung metastases	*n* = 1	1 %
Diffuse lung metastases	*n* = 15	14 %
Lymphatic metastases	*n* = 17	16 %
Bone metastases	*n* = 3	3 %
Hepatic tumor load (median (range), %)	15.7 (1.0–63.0)	
CEA serum level (median (range), ng/ml)	130.1 (2.7–8713.3)	
CA19-9 serum level (median (range), U/ml)	192.7 (0.3–32206.0)	
Radioembolization procedures	*n* = 178	100 %
Bilobar (total liver)	*n* = 12	7 %
Unilobar	*n* = 52	30 %
Sequential lobar	*n* = 114	64 %
Treatment sessions per patient (median (range))	2 (1–5)	
Total activity per patient (median (range), MBq)	1725.0 (200.0–3650)	

Data collection

Follow-up data was acquired until May 2013. The patient database contained a prospective data set including therapies prior to presentation at our institution (surgical resection, chemotherapy and combined immunochemotherapy), tumor markers (Carcinoembryonic antigen, CEA and Cancer antigen 19–9, CA19-9 serum levels), individual patient characteristics (age, sex, Karnofsky index) and imaging aspects (initial staging, tumor distribution and hepatic tumor load). Finally, details of Y90 radioembolization (applied activity, number of treatment sessions and more) were included. Side effects were defined and categorized by the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03).

Statistical analysis

SPSS 21.0 (IBM®, New York, USA) was used for the entire analysis. Descriptive analysis was computed with median and range of continuous variables as well as frequencies of nominal data. Univariate stepwise Cox regression analysis was used to determine factors influencing patient survival. Any factor with a tendency towards significance ($p \leq 0.1$) was included in a multivariate Cox proportional hazard model. Variables demonstrating a significant influence on survival in the multivariate regression analysis were used to create a prognostic score. Binarization of the scoring parameters was based on the median, the discrimination values were then analyzed applying the Kaplan-Meier Method and Log-rank test. All tests were two-sided, statistical significance was assumed at a $p < 0.05$.

Results

Treatment and toxicities

We performed a total of 178 radioembolizations in 106 patients, including 12 whole-liver, 52 unilobar and 114 sequential lobar procedures. This resulted in a median number of 2 treatment sessions per patient (range: 1 – 5). Repeated radioembolizations of a specified liver volume with at least 3 sessions were limited to 8 patients. A median total activity of 1725 MBq (range: 200 – 3650 MBq) was administered per patient. The median tumor load was 15.7 %(range: 1.0 – 63.0 %).

No acute mortality was observed within 30 days post radioembolization. A total of 12 toxicities grade 3 or 4 according to CTCAE 4.02 were observed in 11 patients, see Table 2. Seven patients developed radiation induced

Table 2 Treatment associated toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE 4.03), a total of 12 major toxicities (grade 3 or 4) occurred in 11 patients

Major treatment related toxicities (grade 3 or 4), 12 events in 11 patients:		
Gastric or duodenal ulcer	*n* = 3	(3 %)
Pleural effusion	*n* = 1	(1 %)
Radiation induced cholecystitis	*n* = 1	(1 %)
Radiation induced liver disease (RILD) presenting with	*n* = 7	(7 %)
Refractory ascites	*n* = 6	(6 %)
Liver failure	*n* = 1	(1 %)

liver disease (RILD) with ascites requiring paracentesis ($n = 6$), in one case associated with liver failure without tumor progression ($n = 1$). One patient displayed pleural effusion requiring thoracocentesis. Symptomatic gastric or duodenal ulcers occurred in three patients with subsequent endoscopic interventions. One patient underwent cholecystectomy after developing radiation induced cholecystitis.

Primary outcome and concomitant therapy

Within the observation period, all patients deceased. Hence, no censored patients occur in our survival analyses. The median follow-up was 6.0 months (range: 1.0 – 48.0 months). The median overall survival of all 106 patients was 6.7 months after the first radioembolization as illustrated in the Kaplan-Meier survival curve (Fig. 1). The median progression free survival assessed by RECIST 1.1 was 3.5 months.In the follow-up period after Y90-radioembolization, 13 patients were given monotherapy with newly available antibodies (e.g. panitumumab). Another 9 patients received further cytotoxic chemotherapy following Y90 radioembolization.

Regression analysis

At first, univariate stepwise Cox regression analysis was carried out for patient demographics and individual performance as well as tumor and treatment characteristics.

Regarding patient characteristics, a significant influence on patient survival was found for the Karnofsky index (median 80 %, range 60 – 100 %; $p = 0.014$), but not for age and sex. Prior resection or radiofrequency ablation, the type of systemic therapy and the number of chemotherapy lines before Y90 radioembolization had no significant influence on patient survival.

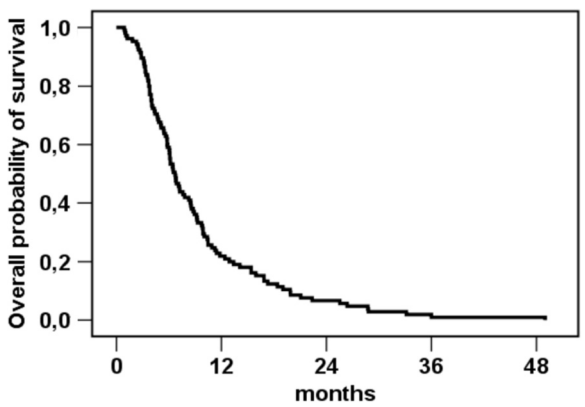

Fig. 1 Kaplan-Meier estimation for overall survival after first radioembolization, all patients ($n = 106$). Since all patients had died by the time of analysis, no censored patients occur in the graph. Median overall survival (OS) was 6.7 months

The hepatic tumor load (median 15.7 %, range 1.0 – 63.0 %) was found a significant factor ($p < 0.001$) while initial tumor staging, grading and extrahepatic manifestations had no significant influence. Furthermore, the serum level of specific tumor markers CEA (median 130.1 ng/ml, range 2.7 – 8713.3 ng/ml) and CA19-9 (median 192.7U/ml, range 0.3 - 32206.0 U/ml) were identified as prognostic factors ($p = 0.002$ and $p < 0.001$, respectively). Detailed parameters of radioembolization (e.g. whole-liver treatment, number of treatment sessions and administered activity of Y90) showed no significant influence. The results of the univariate analysis are summarized in Table 3.

In a second step, all factors with a $p \leq 0.1$ were included in a multivariate Cox regression. In this analysis, significant results were found for the Karnofsky index ($p = 0.037$), hepatic tumor load ($p = 0.001$) and serum levels of CEA and CA19-9 ($p = 0.023$ and $p < 0.001$, respectively). Concomitant bone or lymphatic metastases had no significant influence on the prognosis ($p = 0.083$ and $p = 0.204$, Table 3).

Clinical score

CEA and CA19-9 serum levels, hepatic tumor load and Karnofsky index were further processed to form a prognostic score.

We binarized these prognostic factors approximating their median, identifying patients with:

- tumor load > 20 %,
- CEA level > 130 ng/ml and/or CA19-9 level > 200 U/ml,
- Karnofsky index < 80 %.

Each of these poor prognostics factors was attributed a single point. Complete data was available for 87 patients (82 %).

Corresponding median survival was 13.4 months for patients displaying 0 points ($n = 20$), 8.3 months with 1 point ($n = 26$), 5.8 months with 2 points ($n = 26$) and 4.0 months with 3 points ($n = 15$), respectively (see Fig. 2). The log-rank test confirmed a significant discrimination between the according patient groups ($p < 0.001$).

When summarizing the groups of patients with 0 and 1 point versus 2 and 3 points, the according log-rank test demonstrated a survival of 10.4 months vs. 5.1 months ($p < 0.001$, see Fig. 3).

Discussion

Y90 radioembolization has recently demonstrated its activity in treatment naïve colorectal liver only disease with a liver-only PFS improvement of 8 months when added to a FOLFOX first line treatment regimen [12]. However, the dominant proportion of patients admitted to Y90 radioembolization

Table 3 Cox regression of potential factors to predict survival

Cox regression	Hazard	(95 % CI)	Univariate P	Multivariate P
Age	1.02	(1.00–1.04)	0.239	
Sex'	0.76	(0.50–1.14)	0.179	
Karnofsky index	0.98	(0.95–0.99)	0.014*	0.037**
Resection/RFA'	0.90	(0.56–1.44)	0.658	
Oxaliplatin + 5-FU'	1.44	(0.91–2.26)	0.118	
Irinotecan + 5-FU'	1.41	(0.82–2.46)	0.216	
Capecitabine'	1.24	(0.79–1.94)	0.344	
Bevacizumab'	0.87	(0.58–1.30)	0.492	
Cetuximab'	1.26	(0.85–1.87)	0.243	
Overall chemotherapy lines	1.14	(0.94–1.37)	0.179	
UICC staging	1.01	(0.79–1.30)	0.286	
Tumor grading	0.90	(0.64–1.28)	0.434	
Lung metastases'	1.53	(0.85–2.74)	0.155	
Lymphatic metastases'	1.60	(0.91–2.80)	0.100*	0.204
Bone metastases'	2.51	(0.89–7.13)	0.083*	0.083
Hepatic tumor load	1.05	(1.03–1.06)	<0.001*	0.001**
CEA serum level	1.00	(1.00–1.00)	0.002*	0.023**
CA19-9 serum level	1.00	(1.00–1.00)	<0.001*	<0.001**
Bilobar Y90 RE'	0.89	(0.45–1.77)	0.740	
Unilobar Y90 RE'	0.74	(0.35–1.55)	0.426	
Sequential lobar Y90 RE'	0.82	(0.40–1.66)	0.775	
Y90 RE sessions per patient	0.95	(0.72–1.24)	0.692	
Total activity per patient	1.00	(0.99–1.00)	0.276	

Results in the univariate analysis (*$p < 0.1$) were included in the multivariate analysis (**$p < 0.05$). Binary factors are marked ('), other variables are ordinal or continuous

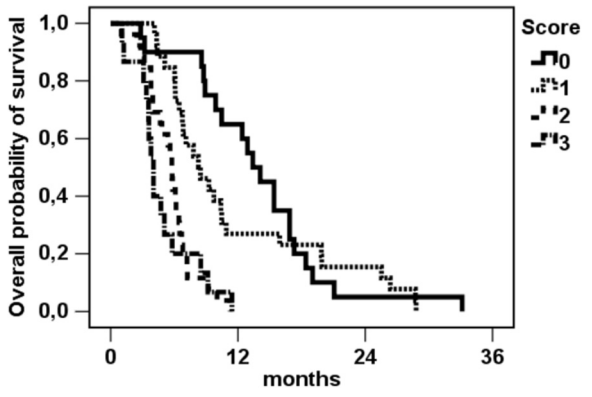

Fig. 2 Kaplan-Meier estimation for overall survival after first radioembolization, strata by score points ($n = 87$). Since all patients had died by the time of analysis, no censored patients occur in the graph. Median OS was 13.4 months (0 points, $n = 20$), 8.3 months (1 point, $n = 26$), 5.8 months (2 points, $n = 26$) and 4.0 months (3 points, $n = 15$), $p < 0.001$

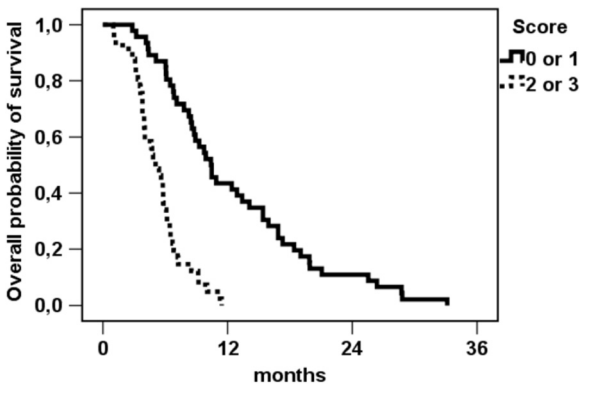

Fig. 3 Kaplan-Meier estimation for overall survival ($n = 87$) after first radioembolization, groups of patients with survival benefit (score of 0/1) vs. no survival benefit (score of 2/3). Since all patients had died by the time of analysis, no censored patients occur in the graph. Median OS was 10.4 months (score 0 or 1) vs. 5.1 months (score 2 or 3), $p < 0.001$

today presents in a salvage setting, with extensive liver tumor load, reduced performance status, chemorefractory disease, and a history of numerous and variable chemotherapy cycles [3, 4, 6]. Our own study contributes data to this patient selection with poor prognosis, with a median Karnofsky of 80 %, a tumor load of 20 %, and chemorefractory dise ase or patients refusing further chemotherapy as a results of toxicity. A total of 81 % patients presented with liver only disease, thirty-five patients (33 %) had undergone 2 lines and 62 patients (58 %) 3 or more lines of chemotherapy.

In this rather dismal patient cohort, the median overall survival of all patients undergoing Y90 radioembolization was 6.7 months. As such, the indication for Y90 radioembolization in our patient group may have been too aggressive, and the survival rate was worse than documented in other series of salvage mCRC Y90 radioembolization. Hendlisz et al. described a median survival of 10 months combining Y90 radioembolization and 5-FU (vs. 7.3 months in 5-FU only); Cosimelli et al. 12.6 months in a single arm cohort; Bester et al. 11.9 months versus 6.6 in control; and Seidensticker et al. 8.3 months versus 3.5 in control [3–6].

As systemic last line treatment, mitomycin C combined with capecitabine has been considered a well-tolerated salvage option for a long time, however associated with very low activity. Lim et al. published a cohort of 21 patients with a median survival of 6.8 months, commenting that there was no definitive contribution to increasing the patients overall survival [13]. Harba et al. reported 7.8 months overall survival in oxaliplatin and irinotecan refractory advanced mCRC [14]. More recently, the CORRECT study comparing cohorts receiving Regorafenib versus placebo reported outcomes of 6.4 versus 5.0 months (HR 0.77) in 760 randomized patients [15], however associated with ≥ grade 3 side effects hand-foot-skin-reaction, fatigue, diarrhea, hypertension and rash in 17 %,10 %, 7 %, 7 % and 6 %, respectively. For panitumumab monotherapy in KRAS wild type patients, van Cutsem et al. reported a reasonable antitumor activity in refractory patients with a median survival of 6.3 months [16].

Even though the pooled overall survival of all patients was poor in our own study, the scoring system derived out of this cohort holds promise for an improved patient selection. The score comprising of Tumor load, CA 19–9 and/or CEA, as well as Karnofsky (TuCK) discriminated two groups of patients with a median survival of 10.4 versus 5.1 months if each factor was attributed 1 point along with summing up patients with 0 and 1 versus 2 and 3 points. It is difficult to interpret whether the poor outcome of patients with 2 and 3 points reflects advanced disease stage or rather an aggressive tumor biology or poor performance status. The survival difference between the two groups (0 and 1 points vs. 2 and 3 points) truly mirrors a composite of multiple, independent factors representing stage, biology and individual patient performance, represented in our study by tumor load, clinical performance status and tumor markers. In addition, patients without these negative factors (TuCK 0) reached a median, overall survival of 13.7 months, which we consider highly favourable in a treatment refractory salvage situation. Interestingly, with the term "liver dominant disease" not clearly defined today, neither lung nor lymph node or bone metastases proved to have a significant impact on survival in our cohort.

Side effects grade 3 and 4 in the overall cohort of patients were limited to 11 of 106 patients (10 %, with 12 events total), indicating that Y90 radioembolization was of moderate toxicity in our patients. Hendlisz et al. in 2010 reported absence of any ≥ grade 3 event in 21 patients randomized to a combination therapy of 5-FU and Y90 radioembolization [5]. These data compare favourably to systemic salvage chemotherapeutic regimen such as by Regorafenib monotherapy with 232 of 500 patients experiencing ≥ grade 3 events, 85 of those discontinuing treatment for side effects (17 %) [15], and even to regimen considered well tolerable such as Capecitabine and mitomycin C with reports of 4 grade 3 or 4 toxicities in 19 patients [13], and 18 grade 3 events in 36 patients [16]. For panitumumab monotherapy, 2 % grade 4 toxicity have been reported, and the most frequent toxicity was skin toxicity [17].

In our patient cohort with a history of extensive chemotherapies and half of the patients displaying a hepatic tumor load >20 %, liver function after radioembolization, i.e. the subsequent development of radiation (radioembolization) induced liver disease (RILD or REILD), is of high interest according to the first description by Sangro et al.[18]. With 7 patients (6 %) displaying clinical symptoms which can be attributed to the development of RILD the incidence is lower than described previously with up to 20 % in a population of mixed tumor entities. We attribute this favorable outcome to the preventive effect of sequential lobar treatment at an interval of 4 to 6 weeks for the left and right liver lobe, as well as single lobar treatments if applicable [10]. In addition, RILD prevention by a drug regimen combining enoxaparin, ursodeoxycholic acid and pentoxiphylline for 8 weeks after treatment may have been beneficial [10, 19].

Conclusion

A score based on Tumor load, CEA and/or CA19-9 serum level as well as the Karnofsky index demonstrated a close association with patient outcome after Y90 radioembolization in the salvage situation. Patients displaying more than 1 point may not benefit from liver directed Y90 radioembolization; in those patients alternative systemic treatments or best supportive care should be considered. In our population with severe liver dominant disease, lung, bone and lymph node metastases had no negative prognostic effect. The role of combined salvage Y90 radioembolization and systemic therapy remains unclear.

Abbreviations
5-FU, 5-fluorouracil; CA19-9, Cancer antigen 19–9; CEA, carcino-embryonic antigen; CT, computed tomography; CTCAE, Common terminology criteria for adverse events; mCRC, metastatic colorectal cancer; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; RE, radioembolization; RECIST, response evaluation criteria in solid tumors; RILD, radiation induced liver disease; SPECT, single photon emission computed tomography; Tc-99 m MAA, Technecium-99 m macro-aggregated albumin; Y90, Yttrium-90

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Availability of data and materials
The dataset(s) supporting the conclusions of this article is (are) included within the article.

Authors' contributions
RD participated in the design of the study, carried out data analysis and statistical work, drafted the manuscript. RS participated in the design and conception of the study and revised the manuscript. GU performed data acquisition and data interpretation. LB helped in the organization of the study and performed data acquisition and interpretation. IGS carried out statistical work and data interpretation. MS participated in the design of the study and helped to revise the manuscript. BG was involved in data interpretation, participated in the editing of the manuscript and helped with the revisions requested by the reviewers. KM participated in the data acquisition and data interpretation. MP and HA participated in the design of the study and performed data interpretation. JR participated in the design of the study, helped drafting the manuscript and carried out the final revision. All authors have given final approval for the manuscript.

Authors' information
Not applicable.

Competing interests
Drs. Ricke, Seidensticker, Mohnike, Garlipp, Pech, Amthauer have received lecture fees and/or travel grants from Sirtex Medical Europe.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Due to the retrospective nature of the analysis, the need for a dedicated ethical approval was waived by the institutional ethics committee of Otto von Guericke University Hospital, Magdeburg.
All patients gave written informed consent to both radioembolization as well as the scientific use of their personal data and publication thereof.

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References

1. van Hazel GA, Bower G, Sharma RA, Blanshard K, Steward WP. Selective internal radiation therapy (SIRT) for liver metastases with concomitant systemic oxaliplatin, 5-fluorouracil and folinic acid: A phase I/II dose escalation study. J Clin Oncol. 2005;23:1–1087.
2. Lim L, Gibbs P, Yip D, Shapiro JD, Dowling R, Smith D, et al. A prospective evaluation of treatment with Selective Internal Radiation Therapy (SIR-spheres) in patients with unresectable liver metastases from colorectal cancer previously treated with 5-FU based chemotherapy. BMC Cancer. 2005;5:132.
3. Bester L, Meteling B, Pocock N, Saxena A, Chua TC, Morris DL. Radioembolisation with Yttrium-90 microspheres: an effective treatment modality for unresectable liver metastases. J Med Imaging Radiat Oncol. 2013;57:72–80.
4. Cosimelli M, Golfieri R, Cagol PP, Carpanese L, Sciuto R, Maini CL, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer. 2010;103:324–31.
5. Hendlisz A, Van den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010;28:3687–94.
6. Seidensticker R, Denecke T, Kraus P, Seidensticker M, Mohnike K, Fahlke J, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol. 2012;35:1066–73.
7. Van Cutsem E, Nordlinger B, Arnold D. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. The European Society for Medical Oncology (ESMO). Ann Oncol. 2014;25 Suppl 6:6–7.
8. Kennedy A, Coldwell D, Sangro B, Wasan H, Salem R. Radioembolization for the treatment of liver tumors general principles. Am J Clin Oncol. 2012;35:91–9.
9. Kennedy A, Nag S, Salem R, Murthy R, McEwan AJ, Nutting C, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys. 2007;68:13–23.
10. Seidensticker R, Seidensticker M, Damm R, Mohnike K, Schütte K, Malfertheiner P, et al. Hepatic toxicity after radioembolization of the liver using (90)Y-microspheres: sequential lobar versus whole liver approach. Cardiovasc Intervent Radiol. 2012;35:1109–18.
11. Salem R, Lewandowski RJ, Gates VL, Nutting CW, Murthy R, Rose SC, et al. Research reporting standards for radioembolization of hepatic malignancies. J Vasc Interv Radiol. 2011;22:265–78.
12. Gibbs P, Sharma N, Findlay M, Ricke J, Gebski V, Van Buskirk M, et al. SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 ± bevacizumab (bev) versus mFOLFOX6 + selective internal radiation therapy (SIRT) ± bev in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol. 2015;33: Suppl 15:3502.
13. Lim DH, Park YS, Park BB, Ji SH, Lee J, Park KW, et al. Mitomycin-C and capecitabine as third-line chemotherapy in patients with advanced colorectal cancer: a phase II study. Cancer Chemother Pharmacol. 2005;56:10–4.
14. Harba AJK, Kegel T, Behrens R, Grothey A, Schmoll HJ. Capecitabine/Mitomycin C as salvage therapy in oxaliplatin and CPT11 refractory advanced colorectal carcinoma. Proc Am Soc Clin Oncol. 2003;22:332.
15. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381:303–12.
16. Chong G, Dickson JL, Cunningham D, Norman AR, Rao S, Hill ME, et al. Capecitabine and mitomycin C as third-line therapy for patients with metastatic colorectal cancer resistant to fluorouracil and irinotecan. Br J Cancer. 2005;93:510–4.
17. Van Cutsem E, Siena S, Humblet Y, Canon JL, Maurel J, Bajetta E, et al. An open-label, single-arm study assessing safety and efficacy of panitumumab in patients with metastatic colorectal cancer refractory to standard chemotherapy. Ann Oncol. 2008;19:92–8.
18. Sangro B, Gil-Alzugaray B, Rodriguez J, Sola I, Martinez-Cuesta A, Viudez A, et al. Liver disease induced by radioembolization of liver tumors: description and possible risk factors. Cancer. 2008;112:1538–46.
19. Seidensticker M, Seidensticker R, Damm R, Mohnike K, Pech M, Sangro B, et al. Prospective randomized trial of enoxaparin, pentoxifylline and ursodeoxycholic acid for prevention of radiation-induced liver toxicity. PLoS One. 2014;9:112731.

Veröffentlichung 8

Cytokines and 90Y-Radioembolization: Relation to Liver Function and Overall Survival.

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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Cytokines and ^{90}Y-Radioembolization: Relation to Liver Function and Overall Survival

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Abstract
Background To evaluate the course of pro- and anti-inflammatory cytokines after ^{90}Y-radioembolization (RE) of liver malignancies and to identify prognosticators for liver-related adverse events and survival.
Methods In 34 consecutive patients with secondary or primary liver tumors scheduled for RE, the following cytokines were measured prior to and 2 h, 3 days, and 6 weeks after RE: interleukin (IL) -1, IL-2, IL-4, IL-6, IL-8, tumor necrosis factor alpha (TNF-α), and interferon-γ. Liver function impairment was defined as an elevation of liver-related laboratory values as graded by CTCAE $\geq$ 2 and/or serum bilirubin $\geq$30 µmol/l and/or development of ascites at 6-week follow-up.
Results Significant changes over time were seen in IL-1 (increase from 0.4 pg/ml (±0.7) at baseline to 1.1 pg/ml (±1.4) 3 days after RE ($p = 0.02$)), and in IL-6 (increase from 16.8 pg/ml (±21.8) at baseline to 54.6 pg/ml (±78.2) 3 days after RE ($p = 0.003$)). Baseline values of IL-6 and IL-8 were independently associated with liver function impairment at follow-up as well as decreased survival with an optimal cutoff at 6.53 and 60.8 pg/ml, respectively.
Conclusion Expected changes in pro- and anti-inflammatory cytokines after RE were shown. Furthermore, baseline values of IL-6 and IL-8 were associated with later liver dysfunction and survival. We hypothesize that these biomarkers are potential prognosticators and might help in patient selection for RE.

Keywords Liver metastases · Hepatocellular carcinoma · Patient selection · Locoregional ablation · SIRT

Introduction

^{90}Y-radioembolization (RE) delivers radionuclide-embedded resin or glass microspheres to liver tumors via the hepatic artery. Upon arterial injection, the microspheres embolize in the tumor vasculature to a greater extent as compared to the normal hepatic parenchyma [1]. RE has shown promising tumor control rates in patients with both primary and secondary liver malignancies. While prospective randomized data are still scarce, diligent analyses of large phase II single-arm cohorts have suggested prognostic benefit, specifically in patients with advanced hepatocellular carcinoma (HCC) and in patients with chemorefractory liver metastases from colorectal cancer [2–12].

However, RE is technically demanding and potentially associated with—among others—liver-related complications (i.e., radioembolization-induced liver disease (REILD)) as outlined in the following. Mechanisms and predisposing factors associated with REILD are still not fully understood [13, 14]. In short, a history of chemotherapy and high applied ^{90}Y activity as well as treatment of the whole liver in one session and subsequent

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chemotherapy in pretreated patients within 2 months after RE are reported to be independently associated with REILD in patients with liver metastases. Patients with HCC are at risk of REILD in case of cirrhosis, low liver volume, and increased bilirubin at baseline [13–15]. In this high-risk group, the incidence of REILD is up to 22.7% (rate of severe REILD of up to 13.3%), whereas patients not demonstrating these characteristics are at low risk of REILD (about 5.5% (severe form in 2.2%)) [13]. The paramount influence of previous damage to the liver parenchyma is demonstrated by the low incidence of REILD (1.2%) in the SIRFLOX study, where the treatment was conducted as a first-line treatment (even though it was applied in a whole-liver setting and was directly followed by chemotherapy) [12].

The pathological hallmark of REILD is a veno-occlusive disease (VOD). Although REILD sometimes resolves under symptomatic treatment, it may progress into a chronical stage with ongoing severe liver impairment with decreased quality of life, restricted possibilities for further tumor therapies and, not uncommonly, reduced survival [14].

To date, no protective agents for the prevention of radiation- or radioembolization-induced liver disease have been proven effective, although some drugs are believed to possibly act protectively (such as low molecular weight heparin, ursodesoxycholic acid, pentoxifylline, and steroids) [16–19]. Thus, in addition to further optimizing the RE procedure, reliable markers are needed to identify patients at risk prior to RE and to individualize RE treatment. Recently, a pre-RE scoring system (the so-called TuCK score) for patients with chemorefractory colorectal liver metastases was published by Damm et al., including tumor load, Karnofsky index, and tumor markers (as identified by a multivariate analysis). The TuCK score was shown to correlate significantly with survival, helping to identify patients who will most likely not benefit from the RE and may unnecessarily be exposed to the risk of treatment-associated morbidity [20].

Cytokines have received increasing attention as potential diagnostic and prognostic markers for preexisting tissue damage (liver inflammation) and cancer involvement [21–27]. In addition to the synthesis of pro-inflammatory cytokines (especially interleukin (IL)-1, IL-6, and tumor necrosis factor alpha (TNF-α)) by resident tissue macrophages (Kupffer cells) in the liver induced by the tumor infiltrates, it is proven that a variety of cancer cells themselves produce cytokines (especially IL-6) [28, 29]. These cytokines might stimulate further inflammation by attraction of inflammatory cells and induce apoptosis of hepatocytes and non-parenchymal cells in a paracrine manner. In several studies, a correlation of pretreatment interleukin levels (especially IL-6), stage of malignant disease (e.g., presence of liver metastases), and survival was shown [21, 22, 24, 26, 27, 30].

Further on, in vivo and in vitro experiments demonstrated a cytokine response after radiotherapy of the liver, with Kupffer cells and sinusoidal endothelial cells in the liver showing an immediate response to radiation consisting of release of TNF-α, IL-6, and IL-1 with following cell–cell interactions and pro-apoptotic and radiosensitizing effects on hepatocytes [31]. Predominantly, this effect has to be rated as a response of the liver parenchyma to the radiation, not of the tumor. However, only two clinical studies reported about cytokine levels after RE treatment [32, 33]. Both studies were able to show a significant increase in pro-inflammatory IL-6 after RE. In both studies, the IL-6 increase in early follow-up was not associated with later toxicities [32, 33].

Analyses of the association of baseline cytokine levels, treatment-associated toxicities, and survival after RE are not available yet.

The objective of the current analysis was to verify the reported data on the change in cytokine levels after RE and to determine whether baseline values or early changes in selected pro- and anti-inflammatory cytokines (IL-1, IL-2, IL-4, IL-6, IL-8, TNF-α, and interferon-γ) may be useful to predict (treatment-related and/or tumor inherent) liver function impairment and/or survival in patients treated with RE.

Materials and Methods

Study Design

During a 14-month period, 60 consecutive patients with secondary or primary liver tumors scheduled for RE as salvage treatment at our institution were included in this exploratory study. Serum levels of distinct cytokines (see section laboratory analyses) were determined in these patients out of routinely drawn blood samples prior to, directly after, 3 days after, and 6 weeks after RE.

The aim of this exploratory study was to evaluate (1) the course of selected cytokines after RE and the potential of these cytokines (pre-RE level or early after RE level) for early prediction of liver function impairment and/or (2) survival. On the basis of these data, a confirmative study will be planned.

The study was approved by the institutional review board, and all patients gave written consent for data evaluation.

Patient Selection and Eligibility Criteria and Patient Characteristics

Of the initially included patients, only patients with complete laboratory work-up (see section laboratory

Table 1 Patient and treatment characteristics

Patient and treatment characteristics	
Variable	Count or mean (±)[a]
Age (*y*, range)	64.6 (55–80)
Sex (f/m)	6/28
Karnofsky (median, range)	80 (70–100)
Tumor entities	
Metastatic disease	22
Colorectal	14
Breast	2
Bladder	2
Others	4[b]
HCC	12
Tumor volume (mL)	325.5 (±360.2)
Liver volume (mL)	2104 (±765)
Tumor load (%)	13.4 (±10.5)
Type of radioembolization	
Whole liver one session	4
Whole liver sequential	21
Unilobar	9
Applied ^{90}Y activity (GBq)	1.32 (±0.57)
Prior chemotherapy	26
>1 Line of chemotherapy	17
Prior liver-targeted therapy[c]	13

HCC hepatocellular carcinoma

[a] If not other indicated

[b] Laryngeal cancer, duodenal cancer, gastric cancer, and bronchial carcinoma

[c] Resection, radiofrequency ablation, transarterial chemoembolization, radiotherapy

analyses) [2 patients excluded] and magnetic resonance imaging (MRI) work-up (see section MRI) [17 patients excluded] were included. Patients treated incompletely [2 patients] as well as patients undergoing other additional liver-targeted local therapies (radiofrequency ablation, local radiotherapy) [1 patient] or chemotherapy [2 patients] in follow-up period were excluded. Additionally, patients with an infection (fever, elevated C-reactive protein, and leukocytes) [2 patients] in the observatory period were excluded. Out of 60 consecutive patients scheduled for a RE of liver malignancies, 34 patients (mean age 63.3 years, 28 men, 6 women) fulfilled the eligibility criteria of the final analysis (Table 1).

Radioembolization

The conduction of RE was performed as described elsewhere [15]. In brief, prior to RE all patients underwent a work-up including clinical status, laboratory, and imaging (CT and MRI of the liver). Further on, a work-up angiography of the vascular supply of the liver was performed using a transfemoral approach. Vessels at risk to lead to an extrahepatic deposition of the microspheres were identified (e.g., gastroduodenal artery, right gastric artery, and other arteries) and embolized, if necessary. This was followed by ^{99m}Tc-MAA injection (150 MBq, Tc-99m-LyoMAA, Covidien, Neustadt/Donau, Germany) at the planned treatment positions. ^{99m}Tc-MAA Lung shunt was quantified in planar imaging, and ^{99m}Tc-MAA distribution in the upper abdomen was visualized by a SPECT (single-photon emission computed tomography) scan (E.CAM 180, Siemens, Erlangen, Germany) including image fusion to CT or MRI from the day before. If an extrahepatic accumulation was visible, a re-angiography was conducted to identify and to embolize or to bridge the according vessel.

Activity of the ^{90}Y resin microspheres (SIR-Spheres®, Sirtex Medical, Lane Cove, Australia) for RE was calculated according to BSA (body surface area) method with activity reduction according to the extent of the lung shunt. In the therapeutic angiography for the RE, the microspheres were injected at the previously defined treatment position(s). The treatment was done in an in-patient fashion, and patients were typically discharged 3 days after the procedure. In order to ameliorate effects of the radiation to liver parenchyma, all patients received low-dose steroids and ursodesoxycholic acid for 6 weeks [13].

The mean applied activity of ^{90}Y was 1.32 GBq (±0.57). In 4 patients, the whole liver was treated in one session; in 21 patients, the treatment of the whole liver was performed in two sessions (sequential one lobe per session) 4–6 weeks apart; and in 9 patients, only one liver lobe was treated. The mean applied activity in these groups was whole liver: 1.7 GBq, sequential: 1.42 GBq, unilobar: 0.9 GBq.

Laboratory Analyses

Serum levels of the following cytokines were measured 1 day prior to and 2 h, 3 days, and 6 weeks after the RE procedure: interleukin (IL) -1, IL-2, IL-4, IL-6, IL-8, tumor necrosis factor alpha (TNF-α) and interferon-γ. One day before and 3 days and 6 weeks after completed RE, the following liver-related and inflammation-related laboratory parameters were determined: alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, alkaline phosphatase [12], albumin, gamma-glutamyltransferase (GGT), glutamate dehydrogenase (GLDH), prothrombin time (INR), cholinesterase (CHE), leukocytes, C-reactive protein (CRP). Deviations from normal values for ALT, AST, total bilirubin, ALP, and albumin were graded according to the common terminology criteria for adverse events (CTCAE), version 4.02.

Magnetic Resonance Imaging

On the day of admission for 99mTc-MAA work-up and 6 weeks after completed RE, an MRI scan (Achieva 1.5T, Philips, Best, the Netherlands) of the liver was performed routinely. The protocol consists of a three-dimensional (3D) T1-weighted gradient recalled echo sequence (time to echo/time to repetition (TE/TR) 2/4 ms, flip angle (FA) 10°, slice thickness 3 mm) before, directly after, and 20 min after application of the hepatocyte-specific contrast media Gd-EOB-DTPA (Gadoxetic acid, Primovist©, Bayer Healthcare, Germany; dosage: 0.025 mmol/kg/body-weight) and a T2-weighted turbo spin echo sequence (TE/TR 90/2100 ms, FA 90°, slice thickness 6 mm) with fat saturation. Two sequences were utilized for this study: the 3D T1 GRE sequence 20 min after application of Gd-EOB-DTPA was used for liver and tumor volumetry prior to RE and for evaluation of tumor response. The T2-weighted TSE sequence with fat saturation was used for detection of ascites prior to and 6 weeks after completed RE. Volumetry measurements (liver, tumor) were taken with the image processing software Osirix (©Antoine Rosset, 2003–2011).

Liver Function Impairment

Liver function impairment was defined as an elevation of liver-related laboratory parameters (ALT, AST, bilirubin, ALP) and/or decreased serum albumin level as graded by CTCAE $\geq$ 2 and/or an elevation of bilirubin of $\geq$30 µmol/l (i.e., $\geq$1.8 mg/dl; corresponds to an elevation of 1.5 time upper limit of normal) and/or development of ascites.

Statistics

Results of continuous data are displayed as means and standard deviations, results of frequency data as counts and percentages. For two-group comparisons of the means, Student's t test was used. Correlations were calculated using a two-sided Pearson's test. Differences between patients undergoing different RE protocols (whole-liver RE, sequential RE, one lobe RE) were assessed by two-sided Kruskall–Wallis tests, and differences by entity and tumor progression were assessed by Fisher's exact test.

The Kaplan–Meier method was used for estimates of overall survival.

Cox regression was used to identify factors significantly associated with overall survival in the study population. For factors with p values of <0.10, Kaplan–Meier curves were calculated along with median survival and interquartile range. Wilcoxon tests were used to evaluate differences between the groups. No imputations for missing values were performed.

The evaluation of potential predictors for liver damage at 6 weeks after completed RE as well as for survival after RE was performed using a logistic regression model, including the factors: baseline cytokine levels and laboratory parameters before first RE, sex, tumor load, cytokine levels and laboratory parameters during follow-up, and the time point. The final model for each factor was chosen by backward variable selection using $p < 0.05$ as selection criterion. Receiver operator characteristic (ROC) analysis was performed on significant predictors to calculate the accuracy and other diagnostic parameters and to determine a cutoff point at the maximum sum of sensitivity and specificity.

For factors with p values of <0.05, Kaplan–Meier curves were calculated using the cutoffs as identified in the ROC analysis along with median survival and interquartile range (IQR). Wilcoxon tests were used to evaluate differences between the groups.

Two-sided p values <0.05 were regarded as statistically significant. This exploratory study was performed to obtain basic data and to generate hypotheses. Therefore, the sample size was based on clinical and practical considerations rather than power calculations.

The statistical analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Cytokine Levels After RE

The means of the specified cytokines at baseline and follow-up are displayed in Table 2. Significant changes over time were seen in interleukin 1 (increase from 0.4 pg/ml (±0.7) at baseline to 1.1 pg/ml (±1.4) 3 days after RE ($p = 0.02$)) and in interleukin 6 (increase from 16.8 pg/ml (±21.8) at baseline to 54.6 pg/ml (±78.2) 3 days after RE ($p = 0.003$)).

Liver Function Prior/After RE

Prior to RE, 5/34 patients showed a grade 2 (3 cases) or grade 3 (2 cases) liver function impairment according to CTCAE-graded laboratory parameters (increase in ALP in all but one cases and AST increase in the remaining patient). Six weeks after completed RE, 10/34 patients showed a grade 2 (9) or grade 3 (1) liver function impairment (increase in bilirubin, 5 cases; increase in ALP, 4 cases; increase in AST, 1 case), with no significant change over time.

Serum bilirubin increased significantly from 11.8 µmol/l (±6.0) prior to RE to 18.0 µmol/l (±17.5) 6 weeks after completed RE ($p = 0.04$), whereas serum albumin and cholinesterase activity showed a slight but significant

Table 2 Cytokine levels at baseline, right after and 3 days, and 6 weeks after radioembolization (RE)

Cytokine	Time point	Mean ± SD	p^a
IL-1 [pg/ml] (<3.9)	Prior to RE	0.4 ± 0.7	
	2 h after RE	0.6 ± 1.5	0.5
	3 days after RE	1.1 ± 1.4	**0.02**
	6 weeks after RE	0.8 ± 1.4	0.15
IL-2 [pg/ml] (<5)	Prior to RE	2.0 ± 1.1	
	2 h after RE	2.1 ± 1.0	0.3
	3 days after RE	2.1 ± 1.3	0.5
	6 weeks after RE	2.3 ± 1.3	0.2
IL-4 [pg/ml] (<10)	Prior to RE	0.24 ± 0.38	
	2 h after RE	0.35 ± 0.50	0.2
	3 days after RE	0.21 ± 0.30	0.8
	6 weeks after RE	0.31 ± 0.42	0.5
IL-6 [pg/ml] (<10)	Prior to RE	16.8 ± 21.8	
	2 h after RE	19.1 ± 23.8	0.4
	3 days after RE	54.6 ± 78.2	**0.003**
	6 weeks after RE	40.7 ± 83.0	0.08
IL-8 [pg/ml] (<10)	Prior to RE	98.6 ± 136.7	
	2 h after RE	82.8 ± 74.5	0.5
	3 days after RE	79.8 ± 71.5	0.4
	6 weeks after RE	112.9 ± 147.5	0.6
TNF-α [pg/ml] (<20)	Prior to RE	2.6 ± 5.0	
	2 h after RE	3.9 ± 6.6	0.2
	3 days after RE	1.6 ± 2.1	0.2
	6 weeks after RE	5.5 ± 10.5	0.2
Interferon-γ [pg/ml] (<10)	Prior to RE	3.5 ± 9.5	
	2 h after RE	4.0 ± 10.3	0.4
	3 days after RE	4.7 ± 15.3	0.4
	6 weeks after RE	10.6 ± 41.2	0.2

Bold values indicate statistical significance ($p < 0.05$)

[a] Statistical testing of cytokine levels after RE to baseline values

decrease (from 39.9 (±3.6) to 37.6 g/l (±5.6)) and from 99.0 (±34.1) to 87.3 µmol/ls (±37.1), respectively) (Table 3).

Prior to RE, 4 patients showed detectable ascites (all grade 1 according to CTCAE). Six weeks after completed RE, ascites was detectable in 16 patients [grade 1 ($n = 12$) and grade 2 ($n = 4$)] ($p = 0.04$).

Liver function impairment according to the definition described above was seen in 8 patients at baseline and in 19 patients 6 weeks after completed RE ($p = 0.005$).

Cancer type, history of chemotherapy, and progression of disease (in 5 cases, all other patient showed a disease control) at follow-up showed no significant correlation with development of liver function impairment.

Overall Survival

Median overall survival after RE was 7.4 months (IQR 5–7.9 months; 95% CI 5.4–10.7 months). Type of RE showed no significant influence on survival (whole-liver RE: 4.8 months, sequential whole-liver RE: 9 months, unilobar RE: 5.8 months, $p = 0.08$).

Cancer type, history of chemotherapy and progression of disease during follow-up showed no significant influence on survival.

Type of RE

No differences between the type of RE treatments performed (whole liver, sequential whole liver, unilobar treatment) were detected for sex ($p = 1.0$), age ($p = 0.703$), cancer type ($p = 0.38$), tumor load ($p = 0.6128$), tumor volume ($p = 0.7674$), liver volume ($p = 0.3237$), overall survival ($p = 0.47$), and disease progression during follow-up ($p = 0.68$). The applied activity was found to differ significantly between patients receiving whole-liver versus unilobar treatment (whole liver: 1.7 GBq, unilobar: 0.9 GBq; $p = 0.0302$), but not for

Table 3 Laboratory parameters, baseline, and follow-up

	Laboratory parameters, baseline, and follow-up		
	Baseline	6-week follow-up	*p* value
Bilirubin (μmol/l)	11.8 (±6.0)	18.0 (±17.5)	**0.04**
Albumin (g/l)	39.9 (±3.6)	37.6 (±5.6)	**0.015**
ALT (μmol/ls)	0.62 (±0.48)	0.58 (±0.46)	0.644
AST (μmol/ls)	0.95 (±0.52)	1.09 (±0.82)	0.352
ALP (μmol/ls)	3.39 (±2.81)	3.13 (±1.58)	0.701
INR	1.03 (±0.14)	1.04 (±0.19)	0.647
GGT (μmol/ls)	4.4 (±3.93)	3.34 (±2.43)	0.177
GLDH (nmol/ls)	168.4 (±121.2)	170.0 (±196.2)	0.385
Cholinesterase (μmol/ls)	99.0 (±34.1)	87.3 (±37.1)	**0.025**
CRP (mg/l)	33.8 (±38.3)	32.5 (±42.0)	0.547
Leukocyte count (Gpt/l)	8.2 (±4.4)	7.6 (±3.3)	0.5

Bold values indicate statistical significance ($p < 0.05$)

ALT alanine transaminase, *AST* aspartate transaminase, *ALP* alkaline phosphatase; *INR* international normalized ratio, *GGT* gamma-glutamyltransferase, *GLDH* glutamate dehydrogenase, *CRP* C-reactive protein

sequential and whole liver or sequential and unilobar. Global differences between the groups with regard to cytokine levels and liver function were not seen; however, specific differences were as follows: At baseline, total bilirubin and IL-2 were significantly elevated in the group of patients eventually receiving unilobar (bilirubin) and whole-liver (IL-2) treatment compared to the other groups ($p = 0.0385$ and $p = 0.0083$, respectively). Two hours after RE, IL-2 and IL-4 levels showed significant differences between groups, with IL-2 being highest and IL-4 being lowest in the whole-liver treatment group ($p = 0.0354$ and $p = 0.0083$, respectively). At later follow-up, only IL-1 (3 days after RE) and GLDH (6 weeks after RE) showed significant differences between the treatment groups, with both parameters being highest in the sequential treatment group ($p = 0.0138$ and $p = 0.0486$, respectively). All other laboratory parameters were not significantly different between treatment groups at any time point.

Threshold Analysis for Prediction of Liver Function Impairment at 6 weeks After RE and Survival

The final model showed a significant influence only for baseline IL-6 and IL-8.

Interleukin 6 at Baseline

The optimal cut point as extracted from the ROC by the Youden Index was 6.53 pg/ml with a sensitivity of 83.3% and specificity of 86.7% (area under the curve (AUC) 87%), corresponding to a positive predictive value of 88% and a negative predictive value of 81% for liver function impairment according to the above-mentioned definition.

The 6.53 pg/ml cutoff for baseline IL-6 was also significantly associated with overall survival in the Cox regression analysis ($p < 0.0001$). Median survival was 13.2 months (Q25: 6 months; Q75: 20.4 months; 95% CI 6–20.4) if baseline IL-6 was ≤6.53 pg/ml, whereas it was 5 months (Q25: 4.1 months; Q75: 7 months; 95% CI 3.2–6.6) in patients with a baseline value of >6.53 pg/ml. (Figure 1a).

Interleukin 8 at Baseline

The optimal cut point as extracted from the ROC by the Youden Index was 60.8 pg/ml with a sensitivity of 66.7% and specificity of 86.7% (AUC 81%), corresponding to a positive predictive value of 86% and a negative predictive value of 68% for liver function impairment according to the above-mentioned definition.

The 60.8 pg/ml cutoff for baseline IL-8 was also significantly associated with overall survival in the Cox regression analysis ($p < 0.0001$). Median survival was 13.2 (Q25: 6.9 months; Q75: 20.4 months; 95% CI 6–20.4) if baseline IL-8 was ≤60.8 pg/ml, whereas it was 5.1 months (Q25: 4.1 months; Q75: 6.7 months; 95% CI 3.2–6.7) in patients with a baseline value of >60.8 pg/ml. (Figure 1b).

mCRC Subgroup Analysis

The results for the largest subgroup, patients with mCRC, were very similar to the overall data with only baseline IL-6 and IL-8 being significantly associated with a liver function impairment in follow-up in the logistic regression with an optimal cutoff of baseline IL-6 and IL-8 at 6.4 and 54.95 pg/ml, respectively. The overall survival, as stratified by these values, was again significantly different with 13.4

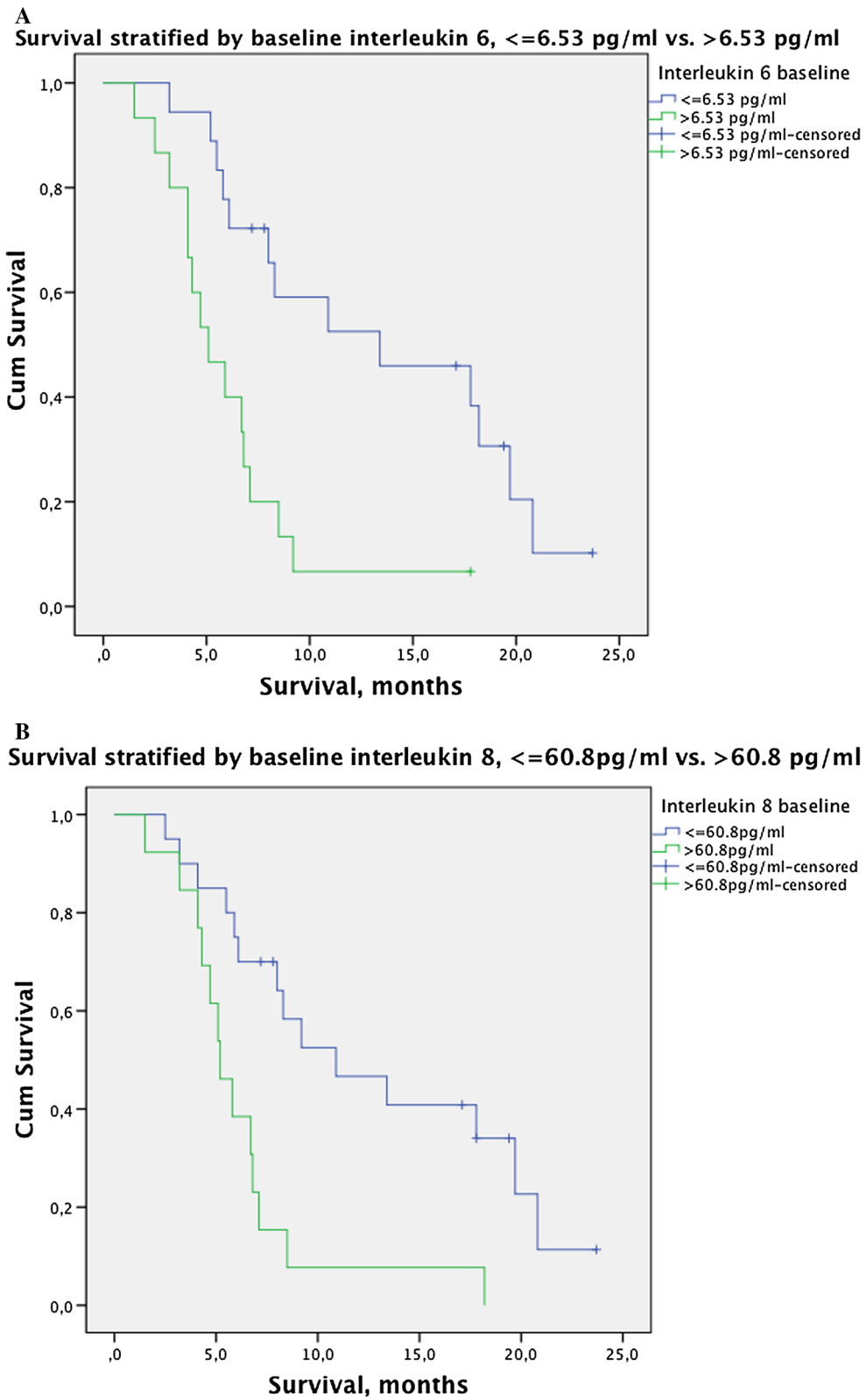

Fig. 1 Kaplan–Meier curve with survival stratified by baseline interleukin 6 (**A**) and baseline interleukin 8 (**B**) values

versus 4.7 months ($p = 0.004$) for IL-6 ($\leq$ vs.>6.4 pg/ml) and 13.4 versus 6.7 months ($p = 0.049$) for IL-8 ($\leq$ vs. >54.95 pg/ml).

In the overall population, IL-6 and IL-8 baseline values correlated significantly but to a weak extent ($p = 0.049$, $R^2 = 0.345$).

Prior exposure to chemotherapy was not associated with elevated IL-6 or IL-8 values (according to calculated threshold values).

A low but significant positive correlation was found between tumor load and the baseline value of IL-6 ($p = 0.013$, $R^2 = 0.43$) and IL-8 ($p = 0.001$, $R^2 = 0.58$). Analysis with regard to tumor entity (HCC and metastatic disease) did not change results except for IL-8 in HCC (IL-6 and IL-8 in metastatic disease: $p = 0.013$, $R^2 = 0.52$ and $p = 0.06$, $R^2 = 0.40$; IL-6 and IL-8 HCC: $p = 0.05$, $R^2 = 0.60$ $p = 0.28$, $R^2 = 0.35$). However, IL-6 and IL-8 were associated with later liver function impairment and survival in the multivariate analysis, not tumor load.

Discussion

In the presented observational study, we sought to determine relevant cytokine levels and changes in RE patients before and during early follow-up after treatment. In line with reported results, we were able to reproduce the increase in pro-inflammatory cytokines (which was most pronounced for IL-6) after RE [32, 33]. In a second step, we were able to identify baseline levels of IL-6 and IL-8 as good predictors of liver function impairment and survival after RE, with a cutoff value of 6.53 pg/ml for IL-6 and 60.8 pg/ml for IL-8, indicating the strong relation between tumor infiltration and induced inflammation. A significant correlation of tumor burden and IL-6 and IL-8 baseline values augments this interpretation. The implementation of these results might help to develop an individualized, and, hence, safer, approach for RE treatment.

RE is gaining increasing importance in the treatment of liver-dominant malignancies (both primary and secondary). To date, most available data have been derived from heavily pretreated patients in a salvage situation; in this scenario, RE can afford a longer progression-free survival and overall survival as compared to best supportive care or systemic chemotherapy. However, clinically relevant liver function impairment (REILD) following RE is a concern [13, 14]. Among others, preexisting damage to the liver parenchyma (e.g., after administration of chemotherapy or in case of underlying liver cirrhosis) is a paramount risk factor for the development of REILD. Up until now, it is still unclear whether this is related to a higher susceptibility of the parenchyma to radiation-induced injury or just to a reduced functional reserve. Several prophylactic regimens are recommended to reduce the risk of a REILD in these patients (sequential lobar treatment, no whole-liver administration, reduced applied yttrium 90 activity, medication with low-dose steroids, ursodeoxycholic acid, enoxaparin, and pentoxifylline) [13, 15, 19]. However, evidence for prophylactic regimens remains low. Furthermore, treatment of REILD is merely symptomatic, whereas a causal treatment is not available. Hence, patient selection is of major interest to identify patients with high probability of liver-related adverse events or short survival prior to RE.

In the literature, cytokines were evaluated in cancer patients with different primaries and their potential was studied to predict outcome and overall survival for different types of therapies (chemotherapy and resection) [21, 22, 24, 26, 27, 30]. In line with our study results, from all tested cytokines mostly IL-6 emerged as the best predictor for outcome and overall survival. Interestingly, our reported cutoff for baseline IL-6 of 6.53 pg/ml is in the range of reported cutoff values for baseline IL-6 prior to oncological treatments other than RE in various types of advanced cancers (with or without liver metastases). Soubrane and colleagues determined a cutoff value for baseline IL-6 of 5 pg/ml to predict survival in patients with metastatic malignant melanoma treated with biochemotherapy (9.7 vs. 24.6 months) [26]. In patients with operable gastric cancer, survival correlated well with preoperative IL-6 with an optimal cutoff at 6.77 pg/ml (overall survival at 24 months 96.2 vs. 80.7%) [22]. Nikiteas et al. were able to show that baseline IL-6 of more than 8 pg/ml was associated with a poorer survival in patients with metastatic colorectal cancer [24]. Several studies were able to show that IL-6 is an independent prognostic parameter in patients with metastatic breast cancer associated with extent of disease and survival. For example, Zhang et al. [27] were able to show a sixfold increased risk of death in patients with IL-6 higher than 5 pg/ml. Interestingly, also patients with HCC and cirrhosis show a comparable pattern. Shao et al. [34] analyzed the outcomes of patients who received sorafenib with metronomic chemotherapy as first-line therapy for advanced HCC and demonstrated that high pretreatment plasma IL-6 or IL-8 levels were associated with poor PFS and OS.

Summary of data shows that in contrast to IL-6, evidence for usability of baseline IL-8 as prognosticator is low.

Tumor load and IL-6/IL-8 showed a low but significant positive correlation, indicating a true association between stage of disease and IL-6 and IL-8 levels. This finding is consistent with results from other studies showing a correlation of IL-6 with tumor burden in metastatic malignant melanoma and breast cancer [23, 27]. If confirmed, IL-6 and IL-8 may have an advantage over tumor volumetry due

to their easy ascertainability. Further on, IL-6 and IL-8 were significantly associated with liver toxicity and overall survival in the multivariate model, not tumor load.

To our knowledge, no other study has reported on the predictive value of baseline cytokines in RE patients. Fernandez-Ros et al. and Wickremesekera et al. were also able to show an increase in IL-6 after RE; however, an analysis regarding the predictive value of cytokines for toxicities during follow-up or survival was not performed [33]. Interestingly, and in line with Fernandez-Ros et al., we were not able to identify a significant change in TNF-α after RE. In contrast to these findings, in vitro experiments have shown a TNF-α release of irradiated Kupffer cells and sinusoidal endothelial cells [31]. However, IL-6 and IL-1 are also known to be important for the initiation of the pro-inflammatory effects in hepatocytes after irradiation, by inducing an acute phase response with subsequent activation of either pro-apoptotic or pro-survival pathways [31].

Several limitations apply to this study, including the small number of patients, which may affect the statistical validity of our results. However, the data acquired in this observational study were used to design a confirmatory study, the aim being to verify the predictive value of IL-6 for side effects and survival following RE.

A further limitation is that patients with different types of cancer were included. Different types and lines of chemotherapy in different cancer types may be associated with different levels of preexisting liver parenchyma damage, resulting in different susceptibility for RE-related side effects. Additionally, livers affected by underlying cirrhosis (as is frequently the case in patients with hepatocellular carcinoma) might react in a different way to RE as non-cirrhotic livers do. To avoid bias induced by underlying liver cirrhosis, patients with a liver function status beyond Child-Pugh grade A were not included in this analysis. Importantly, tumor type was without significant influence on the development of liver function impairment and overall survival, and a subgroup analysis on mCRC population revealed similar results regarding the independent predictive value of baseline IL-6 and IL-8 values on liver function impairment and survival. Furthermore, published data support that increased IL-6 levels are a general finding in malignant liver disease of various origins including HCC in cirrhosis, respectively [21, 22, 24, 26, 27, 30, 34]. A further limitation is that patients with unilobar, whole liver sequential, and whole-liver RE treatments were included. The different amount of applied activity (unilobar vs. whole liver) or the treatment regimen (sequential whole liver vs. whole liver) might have led to a bias. However, both the types of RE and the amount of applied activity were without influence on following liver function impairment and overall survival. This finding is in contrast to published data on adverse events after RE, where the sequential treatment approach was associated with significant less liver function impairment compared to the whole-liver approach [15]. We assume that this difference may be associated with varying definitions of liver function impairment in our and other studies. Further on, influence of the prophylactic coil embolization on cytokine values, especially baseline values, cannot be excluded. However, since other observational studies on patients receiving no RE report about similar magnitudes of cytokines at baseline (as outlined above), we rate this influence as neglectable. Finally, the overall survival after RE is comparatively low in our study cohort, indicating the salvage situation of the treated patients. Thus, transferability of the results to other cohorts treated at an earlier stage of disease is limited.

Conclusions

In this study, we were able to reproduce changes in pro- and anti-inflammatory cytokines after RE. Furthermore, we were able to identify baseline biomarkers (IL-6 and IL-8 baseline values) to be associated with later liver dysfunction and survival. We hypothesize that these biomarkers are potential prognosticators and might help in patient selection for RE.

Compliance with Ethical Standards

Conflict of interest Max Seidensticker reports grants and personal fees from SIRTEX Medical, grants and personal fees from Bayer Healthcare, outside the submitted work. Maciej Powerski, Robert Damm, Maurice Klopffleisch have no conflict of interest. Ricarda Seidensticker reports grants from SIRTEX Medical, personal fees from Bayer Healthcare, outside the submitted work. Benjamin Garlipp reports grants and personal fees from Sirtex medical, outside the submitted work. Holger Amthauer reports grants and other from Sirtex, outside the submitted work. Jens Ricke reports grants and personal fees from Sirtex Medical, personal fees from Siemens, grants from Bayer Healthcare, outside the submitted work. Maciej Pech reports grants and personal fees from Sirtex medical, outside the submitted work.

Ethical Approval The authors state that the study was conducted in compliance with ethical standards.

References

1. Kennedy AS, Nutting C, Coldwell D, Gaiser J, Drachenberg C. Pathologic response and microdosimetry of (90)Y microspheres in man: review of four explanted whole livers. Int J Radiat Oncol Biol Phys. 2004;60(5):1552–63.
2. Bester L, Meteling B, Pocock N, Pavlakis N, Chua TC, Saxena A, Morris DL. Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. J Vasc Interv Radiol. 2012;23(1):96–105.

3. Cosimelli M, Golfieri R, Cagol PP, Carpanese L, Sciuto R, Maini CL, Mancini R, Sperduti I, Pizzi G, Diodoro MG, Perrone M, Giampalma E, Angelelli B, Fiore F, Lastoria S, Bacchetti S, Gasperini D, Geatti O, Izzo F. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer. 2010;103(3):324–31.
4. Hilgard P, Hamami M, Fouly AE, Scherag A, Muller S, Ertle J, Heusner T, Cicinnati VR, Paul A, Bockisch A, Gerken G, Antoch G. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology. 2010;52(5):1741–9.
5. Kennedy AS, McNeillie P, Dezarn WA, Nutting C, Sangro B, Wertman D, Garafalo M, Liu D, Coldwell D, Savin M, Jakobs T, Rose S, Warner R, Carter D, Sapareto S, Nag S, Gulec S, Calkins A, Gates VL, Salem R. Treatment parameters and outcome in 680 treatments of internal radiation with resin 90Y-microspheres for unresectable hepatic tumors. Int J Radiat Oncol Biol Phys. 2009;74(5):1494–500.
6. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, Paprottka PM, Fiore F, Van Buskirk M, Bilbao JI, Ettorre GM, Salvatori R, Giampalma E, Geatti O, Wilhelm K, Hoffmann RT, Izzo F, Inarrairaegui M, Maini CL, Urigo C, Cappelli A, Vit A, Ahmadzadehfar H, Jakobs TF, Lastoria S. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011;54(3):868–78.
7. Seidensticker R, Denecke T, Kraus P, Seidensticker M, Mohnike K, Fahlke J, Kettner E, Hildebrandt B, Dudeck O, Pech M, Amthauer H, Ricke J. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc IntervRadiol. 2012;35(5):1066–73.
8. Hendlisz A, Van den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, De Keukeleire K, Verslype C, Defreyne L, Van Cutsem E, Delatte P, Delaunoit T, Personeni N, Paesmans M, Van Laethem JL, Flamen P. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010;28(23):3687–94.
9. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, Sato KT, Wang E, Gupta R, Benson AB, Newman SB, Omary RA, Abecassis M, Kulik L. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010;138(1):52–64.
10. Memon K, Kulik L, Lewandowski RJ, Mulcahy MF, Benson AB, Ganger D, Riaz A, Gupta R, Vouche M, Gates VL, Miller FH, Omary RA, Salem R. Radioembolization for hepatocellular carcinoma with portal vein thrombosis: impact of liver function on systemic treatment options at disease progression. J Hepatol. 2013;58(1):73–80.
11. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, Mulcahy MF, Baker T, Abecassis M, Miller FH, Yaghmai V, Sato K, Desai K, Thornburg B, Benson AB, Rademaker A, Ganger D, Kulik L, Lewandowski RJ. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2016;151(6):1155e2–1163e2.
12. van Hazel GA, Heinemann V, Sharma NK, Findlay MP, Ricke J, Peeters M, Perez D, Robinson BA, Strickland AH, Ferguson T, Rodriguez J, Kroning H, Wolf I, Ganju V, Walpole E, Boucher E, Tichler T, Shacham-Shmueli E, Powell A, Eliadis P, Isaacs R, Price D, Moeslein F, Taieb J, Bower G, Gebski V, Van Buskirk M, Cade DN, Thurston K, Gibbs P. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin Oncol. 2016;34(15):1723–31.
13. Gil-Alzugaray B, Chopitea A, Inarrairaegui M, Bilbao JI, Rodriguez-Fraile M, Rodriguez J, Benito A, Dominguez I, D'Avola D, Herrero JI, Quiroga J, Prieto J, Sangro B. Prognostic factors and prevention of radioembolization-induced liver disease. Hepatology. 2013;57(3):1078–87.
14. Sangro B, Gil-Alzugaray B, Rodriguez J, Sola I, Martinez-Cuesta A, Viudez A, Chopitea A, Inarrairaegui M, Arbizu J, Bilbao JI. Liver disease induced by radioembolization of liver tumors: description and possible risk factors. Cancer. 2008;112(7):1538–46.
15. Seidensticker R, Seidensticker M, Damm R, Mohnike K, Schuette K, Malfertheiner P, Van Buskirk M, Pech M, Amthauer H, Ricke J. Hepatic toxicity after radioembolization of the liver using Y-90-microspheres: sequential lobar versus whole liver approach. Cardiovasc Interv Radiol. 2012;35(5):1109–18.
16. Essell JH, Schroeder MT, Harman GS, Halvorson R, Lew V, Callander N, Snyder M, Lewis SK, Allerton JP, Thompson JM. Ursodiol prophylaxis against hepatic complications of allogeneic bone marrow transplantation. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1998;128(12 Pt 1):975–81.
17. Or R, Nagler A, Shpilberg O, Elad S, Naparstek E, Kapelushnik J, Cass Y, Gillis S, Chetrit A, Slavin S, Eldor A. Low molecular weight heparin for the prevention of veno-occlusive disease of the liver in bone marrow transplantation patients. Transplantation. 1996;61(7):1067–71.
18. Park SH, Lee MH, Lee H, Kim HS, Kim K, Kim WS, Jung CW, Im YH, Yoon SS, Kang WK, Park K, Park CH, Kim SW. A randomized trial of heparin plus ursodiol vs. heparin alone to prevent hepatic veno-occlusive disease after hematopoietic stem cell transplantation. Bone Marrow Transp. 2002;29(2):137–43.
19. Seidensticker M, Seidensticker R, Damm R, Mohnike K, Pech M, Sangro B, Hass P, Wust P, Kropf S, Gademann G, Ricke J. Prospective randomized trial of enoxaparin, pentoxifylline and ursodeoxycholic acid for prevention of radiation-induced liver toxicity PLoS ONE. 2014;9(11):e112731.
20. Damm R, Seidensticker R, Ulrich G, Breier L, Steffen IG, Seidensticker M, Garlipp B, Mohnike K, Pech M, Amthauer H, Ricke J. Y90 Radioembolization in chemo-refractory metastatic, liver dominant colorectal cancer patients: outcome assessment applying a predictive scoring system. BMC Cancer. 2016;16(1):509.
21. Chung YC, Chang YF. Significance of inflammatory cytokines in the progression of colorectal cancer. Hepatogastroenterology. 2003;50(54):1910–3.
22. Kim DK, Oh SY, Kwon HC, Lee S, Kwon KA, Kim BG, Kim SG, Kim SH, Jang JS, Kim MC, Kim KH, Han JY, Kim HJ. Clinical significances of preoperative serum interleukin-6 and C-reactive protein level in operable gastric cancer. BMC Cancer. 2009;9:155.
23. Mouawad R, Benhammouda A, Rixe O, Antoine EC, Borel C, Weil M, Khayat D, Soubrane C. Endogenous interleukin 6 levels in patients with metastatic malignant melanoma: correlation with tumor burden. Clin Cancer Res. 1996;2(8):1405–9.
24. Nikiteas NI, Tzanakis N, Gazouli M, Rallis G, Daniilidis K, Theodoropoulos G, Kostakis A, Peros G. Serum IL-6, TNFalpha and CRP levels in Greek colorectal cancer patients: prognostic implications. World J Gastroenterol. 2005;11(11):1639–43.
25. Salgado R, Junius S, Benoy I, Van Dam P, Vermeulen P, Van Marck E, Huget P, Dirix LY. Circulating interleukin-6 predicts survival in patients with metastatic breast cancer. Int J Cancer. 2003;103(5):642–6.
26. Soubrane C, Rixe O, Meric JB, Khayat D, Mouawad R. Pretreatment serum interleukin-6 concentration as a prognostic

factor of overall survival in metastatic malignant melanoma patients treated with biochemotherapy: a retrospective study. Melanoma Res. 2005;15(3):199–204.
27. Zhang GJ, Adachi I. Serum interleukin-6 levels correlate to tumor progression and prognosis in metastatic breast carcinoma. Anticancer Res. 1999;19(2B):1427–32.
28. Knupfer H, Preiss R. Significance of interleukin-6 (IL-6) in breast cancer (review). Breast Cancer Res Treat. 2007;102(2):129–35.
29. Knupfer H, Preiss R. Serum interleukin-6 levels in colorectal cancer patients–a summary of published results. Int J Colorectal Dis. 2010;25(2):135–40.
30. De Vita F, Orditura M, Auriemma A, Infusino S, Roscigno A, Catalano G. Serum levels of interleukin-6 as a prognostic factor in advanced non-small cell lung cancer. Oncol Rep. 1998;5(3):649–52.
31. Richter C, Seco J, Hong TS, Duda DG, Bortfeld T. Radiation-induced changes in hepatocyte-specific Gd-EOB-DTPA enhanced MRI: potential mechanism. Med Hypotheses. 2014;83(4):477–81.
32. Wickremesekera JK, Chen W, Cannan RJ, Stubbs RS. Serum proinflammatory cytokine response in patients with advanced liver tumors following selective internal radiation therapy (SIRT) with (90)Yttrium microspheres. Int J Radiat Oncol Biol Phys. 2001;49(4):1015–21.
33. Fernandez-Ros N, Inarrairaegui M, Paramo JA, Berasain C, Avila MA, Chopitea A, Varo N, Sarobe P, Bilbao JI, Dominguez I, D'Avola D, Herrero JI, Quiroga J, Sangro B. Radioembolization of hepatocellular carcinoma activates liver regeneration, induces inflammation and endothelial stress and activates coagulation. Liver Int. 2015;35(5):1590–6.
34. Shao YY, Hsu CH, Huang CC, Cheng AL. Use of plasma angiogenesis-related factors to investigate the association of interleukin 8 and interleukin 6 levels with efficacy of sorafenib-based antiangiogenic therapy in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2011;29(suppl 4):199.

Veröffentlichung 9

Percutaneous radiofrequency ablation in the treatment of pulmonary malignancies: efficacy, safety and predictive factors.

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Research Paper

Percutaneous radiofrequency ablation in the treatment of pulmonary malignancies: efficacy, safety and predictive factors

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ABSTRACT

Purpose: The purpose of this study was to evaluate the efficacy, safety and predictive factors of RFA of primary and secondary lung malignancies.

Patients and Methods: 79 patients with 129 primary and secondary lung malignancies were enrolled in a retrospective study. We treated 74 pulmonary metastases of colorectal cancer, 13 malignant melanoma lesions, 13 renal cancer metastases, 5 primary lung malignancies and 24 tumors of other different entities. All patients were considered to be unsuitable candidates for surgery, radiotherapy or chemotherapy. The primary endpoint was local tumor control, secondary endpoints were overall survival, safety and predictive factors, e.g. distance to pleura, vessels and bronchi.

Results: The median tumor size was 1.2 cm (0.5–3.0 cm). After a median follow-up of 14 months (3–81 months), the LTC was 85.3 %. There were 34 lesions (26.4%) with complete remission, 48 (37.2 %) partial remission, 28 (21.7%) stable disease and 19 lesions (14.7%) with progressive disease. We evaluated an OS of 27 months. Pneumothorax in 19 cases (14.7%) and pleural effusion in 2 cases (1.6 %) were the leading complications (CTCAE, 5 grade III adverse events). The only significant influence regarding the outcome after RFA was the initial tumor size (p = 0.01). Distance to vessel, bronchi, and pleura showed no significant effect (p = 0.81; p = 0.82; p = 0.80).

INTRODUCTION

Surgical resection is the standard of care for early stage NSCLC, with overall 5-year survival rates ranging from 40% to 67% for stage I [1, 2] and from 25% to 55% for stage II [1]. Pulmonary metastasectomy is also the treatment of choice for lung metastases. However, the role of surgical resection is determined by the location, the number of the pulmonary lesions, different co-morbidities and advanced disease of the patients [3].

For high-surgical-risk patients, several studies reported promising results for minimally invasive therapies such as image-guided radiofrequency ablation (RFA) and laser-induced thermo-ablation (LITT) [4–7]. In the last years, newer local-ablative treatments like microwave ablation (MWA) and high-dose-rate (HDR) brachytherapy gained success in the treatment of pulmonary lesions. Considering organ-specific and tissue-related conditions in the lung that affect technical success, percutaneous tumor ablation is assured to be a feasible, safe and effective minimally invasive procedure [5, 8, 9].

Numerous studies have analyzed the outcome of RFA in the treatment of lung malignancies and have shown promising results regarding efficacy and safety. The aim of this single-center university study was, besides the assessment of efficacy and safety, the evaluation of the influence of possible predictive factors on outcome and safety.

RESULTS

Treatment characteristics and technical success

We treated 79 patients with 129 lung tumors in 117 sessions. The median diameter of all 129 lung tumors was 1.2 cm (0.5 to 3.0 cm; mean 1.3 cm). 41 lesions ranged from 0.5–1 cm in tumor size, 74 lesions ranged from 1–2cm and 14 lesions ranged from 2–3 cm. Regarding the distance to a pulmonary vessel, 14 tumor lesions were directly adjacent (0–0.5 cm), 82 lesions showed a distance between 0.5 to 2 cm and 33 appeared > 2 cm. Regarding the distance to a bronchus, 8 lesions were 0–0.5 cm in distance, 61 were located 0.5–2 cm from the bronchus and 60 showed relevant distance (> 2 cm).

47 malignancies (36.4%) were spread in the upper lobe, 12 tumors (9.3%) were located in the intermediate lobe and 70 targets (54.3%) were part of the lower lobe in both lungs. Relating to the neighboring pleura, 10 lesions were directly adjacent to the pleura (0–0.5 cm) and 119 showed a distance > 1 cm.

Treatment was successfully completed in all 117 ablation procedures (100%) without any premature interruption. The median time of the complete procedure was 17 minutes (range, 10–30 minutes).

Local tumor control, overall survival and predictive factors

There was a median follow-up period of 14 months (3–81 months) to examine LTC as the primary endpoint of this study. LTC was achieved in 110 target tumors (85.3%) (Figure 1). Regarding to RECIST 1.1, 34 lesions (26.4%) showed complete remission (CR), 48 tumors (37.2%) showed partial remission (PR), 28 cases (21.7%) were rated as stable disease (SD) and 19 (14,7%) treated lesions which resulted in progressive disease (PD) (Table 1).

Validation of possible predictive factors stratifying the survival curves indicated that LTC was decreased in cases of larger initial tumor size. Lung malignancies between 2 and 3 cm in longest diameter presented local progression in 28.6%, 1 to 2 cm tumors in 16.2% and lesions ranging from 0.5 to 1 cm in only 7.3% (Figure 2A, Table 1). Size class demonstrated a significant influence ($p = 0.013$, log-rank; $p = 0.029$, Breslow) on local tumor progression. Overall survival was not significantly affected by initial target lesion size ($p = 0.659$, log-rank). Patients with an initial tumor size from 0.5 to 1 cm showed a median OS of 26.2 months; in 1 to 2 cm and 2 to 3 cm tumor sizes a median OS of 26.0 and 16,3 months was found respectively (Figure 2B, Table 1). Cox regressions confirmed initial target lesion size as an important impact factor ($p = 0.012$).

Ten pulmonary lesions were adjacent to the pleura (≤ 1 cm), while 119 showed a distance ≥ 1 cm. 2 of the 10 pleural lesions showed a local recurrence. 17 of 119 lesions with a distance ≥ 1 cm showed a local recurrence (Figure 3A, Table 1). There was no significant influence regarding the distance of pleura to the local recurrence ($p = 0.807$, log-rank).The distance from vessels and bronchi showed no statistically significant effect on local recurrence rate ($p = 0.812$, log-rank; $p = 0.820$, log-rank) (Figure 3B, 3C; Table 1).

The median measurable diameter of a vessel located near a treated lesion was 0.4 cm (mean, 0.6, 0.1–3 cm) and the median measurable diameter of an adjacent bronchus was 0.4 cm (mean, 0.5, 0.2–2 cm). These possible relevant parameters showed no significant influence.

The median OS after treatment was obtained after a period of 27 months (Figure 4A). The median OS in the group of local recurrence was only 14.9 months (Figure 4B). Local recurrence showed a significant influence regarding the overall survival ($p = 0,020$, log-rank). In a subgroup analysis, we evaluated the OS of the patients with 74 treated colorectal pulmonary metastases. In these cases, the median OS was 13 months (Figure 5A) and the median time to recurrence was 8 months (Figure 5B).

Safety and adverse events

Overall, pneumothorax in 19 cases (14.7%) and pleural effusion in 2 patients (1.6%) were the leading complications in this series. Minor complications were recorded after 18 procedures (14%) (Tables 2, 3). There were 5 major complications (3.9%) in conjunction with pneumothorax and pleural effusion that required treatment via placement of a small-bore catheter in one patient (0.8%) and a larger chest tube placement in 2 patients (1.6%), rated as CTCAE Grade II and III (Tables 3, 4). One patient suffered from a painful skin burn (0.8%) as a major complication from cutaneous adhesive electrode grounding during the ablation session, rated as CTCAE Grade III. A postprocedural infection caused a pulmonary abscess cavity in one patient (0.8%) requiring systemic antibiotic therapy, rated as CTCAE Grade II. Our study showed no Grade 4 and 5 CTCAE due to the ablation.

DISCUSSION

Different local therapies are available for patients with NSCLC and secondary oligometastatic disease, including stereotactic body radiation therapy (SBRT, 97.6% LTC rate) [10], stereotactic radiosurgery with CyberKnife (95% LTC rate) [11] as well as image-guided thermal and non-thermal tumor ablation [12, 13]. Numerous studies in the literature demonstrate the outcome of RFA in pulmonary lesions. A most recently published study by Nour-Eldin et al. compared LITT, RFA and MWA in the treatment of non-colorectal lung metastases. The study reported a LTC rate of 70.6% for LITT, 79.3% for RFA and 90.5% for MWA. Pneumothorax was detected in 22.73% for LITT, 14,23%

for RFA and 22.16% for MWA [14]. Regarding those satisfying results, RFA still has its impact as an ablative oncologic therapy method.

The presented study, with a LTC of 85.3% and a complication rate of 14% minor complications and 4% major complications, could contribute and widely confirm the data in the literature. Yamakado et al. achieved a LTC of 83% in 155 treated lung metastases from colorectal cancer in a Japanese multicenter study [15]. A study on 153 patients by Simon et al. differentiated between large and small lesions (< 3 cm) showing an important positive influence on survival curves in conjunction with smaller lesions [6]. Those results are consistent with our study, demonstrating a significant influence of tumor size on local tumor progression. De Beare et al. reported the largest series today of RFAs in 1037 lung metastases from a variety of primary sites with a median OS of 62 months. The location of primary disease, disease-free interval (DFI), size > 2 cm, and number of metastases were significantly associated with OS in uni- and multivariate regression analyses [16].

For lung metastases, OS rates after RFA are within the range of best results obtained after surgical resection, with 5-year OS rates of 53.5% for Iida et al. [17] in a multicenter registry, in between 27% and 68% in a meta-analysis by Gonzalez et al. [18]. The median OS of our population was 27 months. Regarding the tumor size, OS was quite similar in the patient group 0.5–1 cm (26.2 months) and 1–2 cm (26.0 months). Patients with a treated size of 2–3 cm showed a median overall survival of 16.3 months. The subgroup of patients with colorectal cancer had a median OS of 13 months. The better outcomes obtained by de Baere et al. are explained by the restricted inclusion criteria, resulting in more favorable predictive factors.

Various research have demonstrated efficient LTC regarding small tumor size, but there are only few studies that evaluate the influence of adjacent vessels and bronchi, the distance to the pleura and the diameter of nearby vessels and bronchi, as analyzed in the presented study.

Contrary to other studies, neither contact to vessels and bronchial tubes, nor vessel and bronchi diameter showed any influence on treatment success in our study.

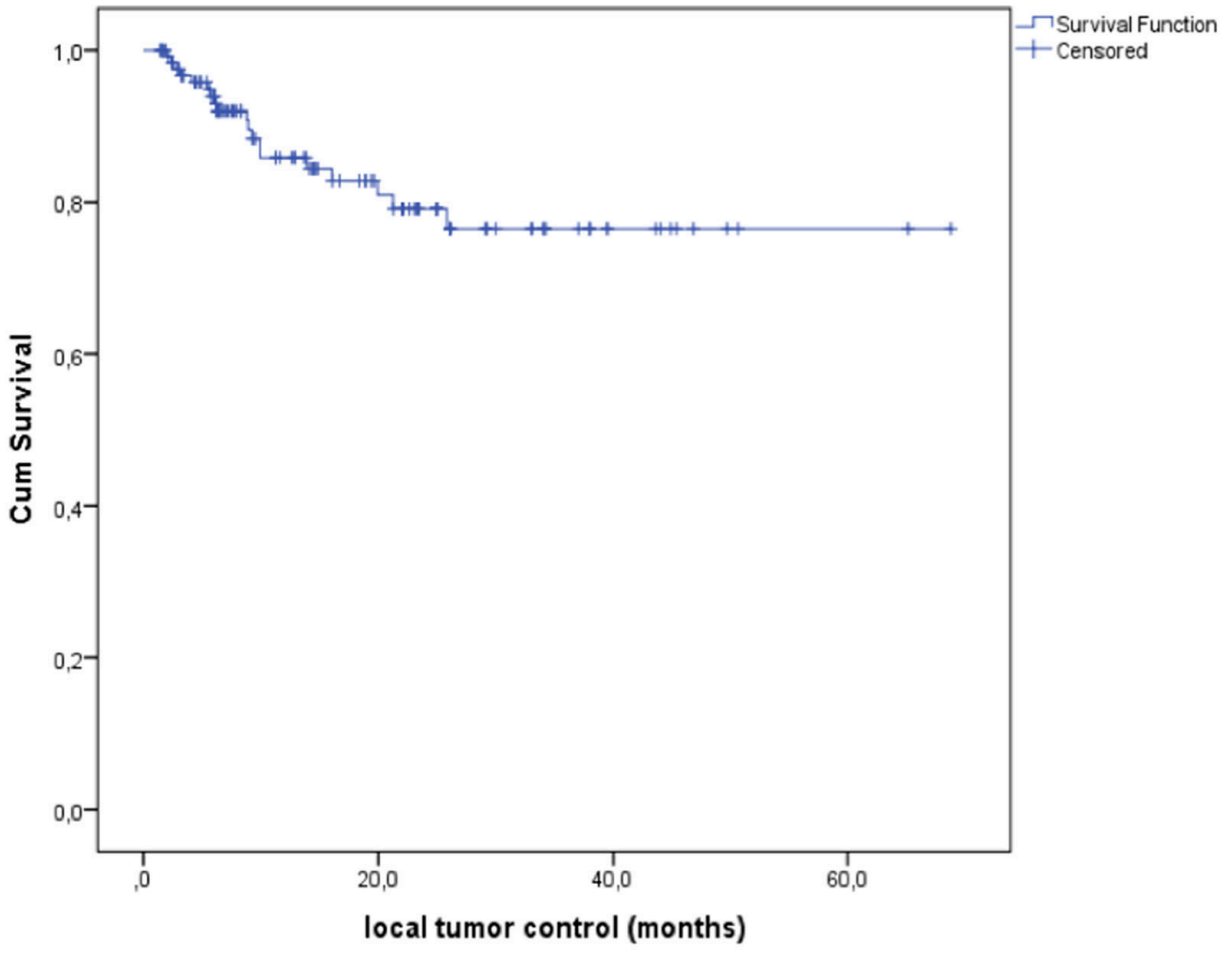

Figure 1: Local tumor control (LTC) was 85.3% after percutaneous CT-guided radiofrequency ablation (RFA) of primary and secondary pulmonary malignancies.

For example, Schneider et al. [19] detected lung neoplasms in a central or hilar location most frequently occurring local 'heat sink effect', and viable tumor cells next to peripheral vessels remaining after ablation procedures by histologic proof.

Histological type as another important factor Hiraki et al. [20] have been considered without statistical validation. A univariate analysis by Garetto et al. [7] documented lower LTC for the treatment of NSCLC compared to pulmonary metastases. In view of the fact that our study counted just 5 patients with NSCLC, our series was inappropriate to undergo statistically significant subgroup analysis, which has to be noted as a limitation.

In our study, we recorded minor complications in 14% and major complications in 4%, without worsening of pulmonary function or CTCAE Grade IV or V complications. Other series stated a similar safety profile with pneumothorax and pleural effusion as the most frequent complications [5, 7]. Periprocedural mortality rate was less than 1% [21] and periprocedural morbidity varied between 15.5% and 55.6% in the literature [22, 23]. Major complications ranged from 8% to 12% [22, 23] in former clinical trials. In the majority of cases, complications after RFA were minor. Nevertheless, rare and serious complications can occur, so radiologists should be familiar with different types of complications. Quick management is essential for a successful treatment. In individual cases, infection or hemorrhage occurred from cavity formation due to tumor colliquation or postinterventional pneumonia stated in up to 30% of cases [24]. Skin burns around the grounding pads as reported in one patient from our series was described in correlation with monopolar radiofrequency ablation. Thus, temperature monitoring at the grounding pads during the procedure is necessary [25].

A prospective multicenter trial from Japan in 2016 analyzed the incidence and grade of AEs using the CTCAE in 33 patients. Two patients showed pleural effusion, which was rated as CTCAE Grade III. One patient had a transient hypoxia with SaO_2 < 88%. Pneumothorax occurred in 12 of 33 patients (36%). Two of them needed a chest tube placement (6.7%). Gobara et al. hypothesized that the observed incidence was due to a high proportion of the patient population having a previous history of thoracic surgery. They claimed that the absence of prior surgical operations might be a risk factor for chest tube placement for pneumothorax [26].

Our study had some limitations. This retrospective analysis was based on a heterogeneous group comprising both primary and secondary lung neoplasms and different former and adjunctive therapies such as chemo- and radiotherapy with unknown influence on the treatment success. Moreover, follow-up visits only consisted of image-guided assessment associated with lesion size, lesion geometry and lesion enhancement, without consideration of histologic proof for treatment completeness. CT scans were related with different patient positioning in the image plane for axial imaging. Other studies evaluated the outcome by using FDG-PET/CT to assess treatment outcomes [27, 28]. With regards to overall survival endpoint, life quality assessment would have been interesting to complete the evaluation of achievements.

Despite these limitations, this study was able to confirm technical success, efficacy and safety of RFA in the treatment of pulmonary malignancies according to other clinical trials in recent years. Furthermore, a feature of this study was the evaluation of different predictive factors, influencing the clinical outcome. In contrast to the distance to pleura, vessel or bronchus, and the vessel and bronchus diameter, the tumor size had a significant influence. This finding underlines the necessity of further technical development of RF technology in the future to improve this already well established and well tolerated method.

The results of the presented study contribute to the statement that in the future lung surgery for small-

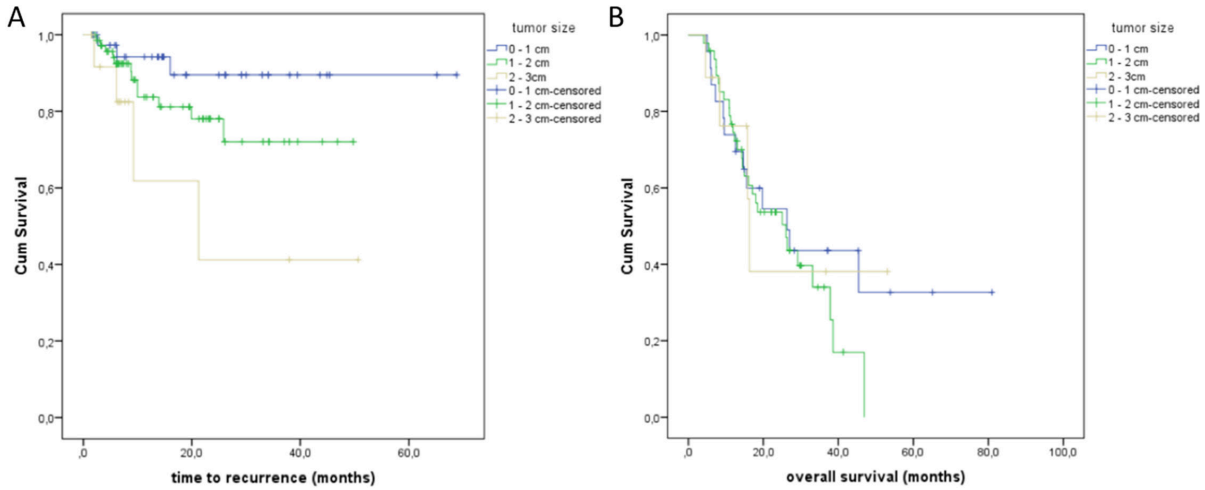

Figure 2: (**A**) Time to recurrence regarding the tumor size of the treated lung malignancies. (**B**) Overall survival (OS) depending on the tumor size; patients with tumor size of 0.5–1 cm showed a median OS of 26.2 months; patients with a tumor size of 1–2 cm and a median OS of 26.0 months; patients with a tumor size of 2–3 cm and a median OS of 16.3 months.

size oligometastatic lung disease will be replaced by low-invasive techniques in selected patients [29]. Future treatment strategies should combine surgical, systemic and interventional options for individual patient-tailored success.

MATERIALS AND METHODS

Patient characteristics and study design

This retrospective single-center study is based on a sample of 79 patients with 129 pulmonary tumor lesions treated within a period of 6 years at a German university clinic (Table 4). Included in the study were 47 men (60%) and 32 women (40%) with a median age of 65.1 years (range 36–83 years). All patients exhibited primary and secondary lung malignancies. In detail, we treated 74 metastases of colorectal cancer, 13 malignant melanoma lesions, 13 renal cancer lesions, 5 primary lung malignancies and 24 tumors of different entities. Pulmonary target lesions ranged from 0.5 to 3.0 cm (median 1.2 cm).

Indication was determined on the basis of multidisciplinary assessment with participation by an interventional radiologist, oncologist, surgeon and pathologist. Inclusion criteria for the ablation were: (a) patients with inoperable pulmonary lesions, (b) poor candidates for surgery due to medical conditions or unsuitable candidates due to advanced cancer related morbidities, (c) patients considered unfit for radiotherapy or chemotherapy, (d) lesions with a maximal axial diameter < 4 cm, (e) pulmonary tumor lesions infiltrating the chest or mediastinal structures and (f) Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2 and platelet counts > than 100 × 10^9/L.

Exclusion criteria were: (a) patients considered high-risk for RFA due to major comorbidities, (b) more than three lesions per lung, (c) ECOG performance status of more than 2 and (d) platelet counts less than or equal to

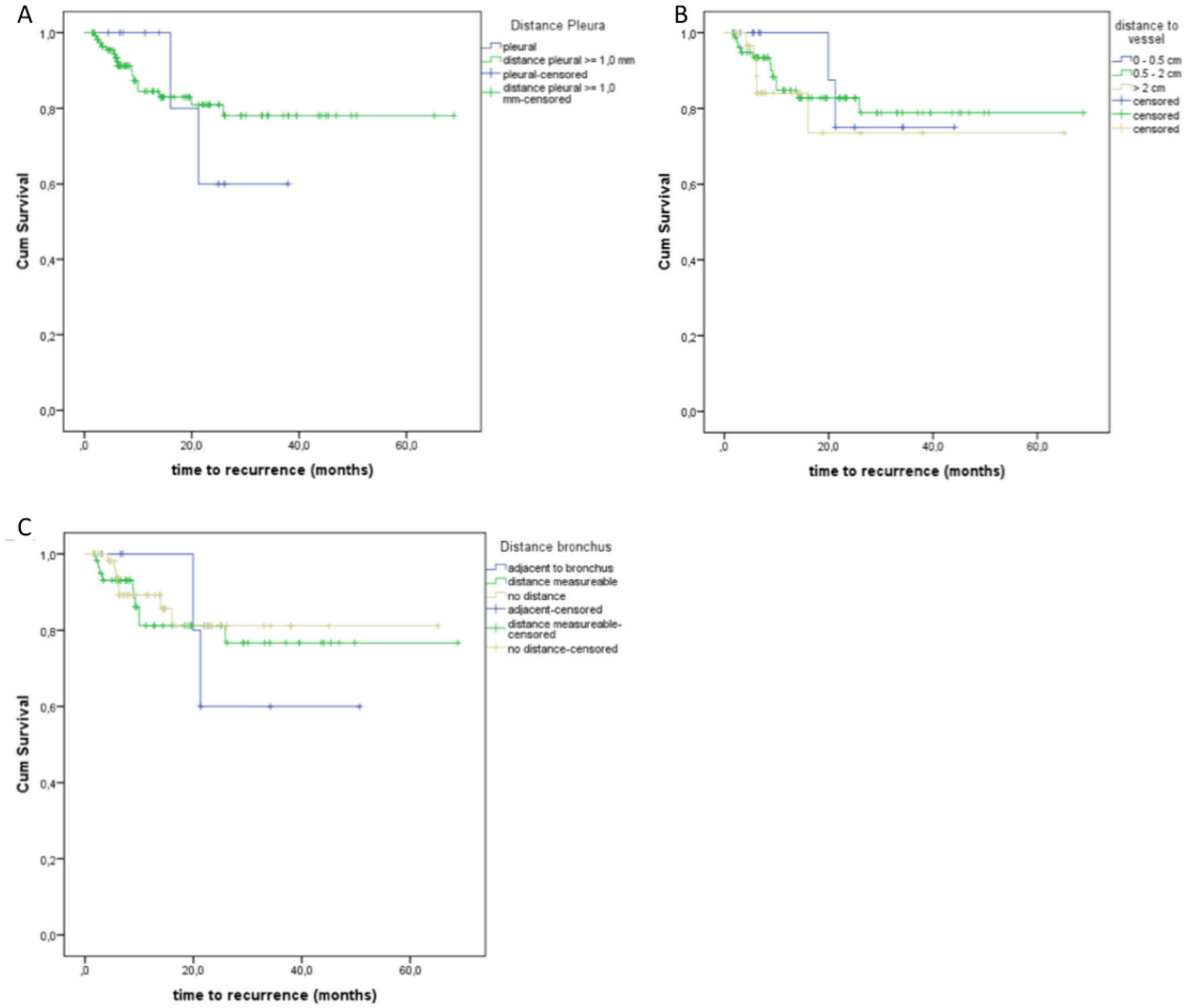

Figure 3: (**A**) Local recurrence regarding the influence of the distance to the pleura. (**B**) Time to recurrence depending on the distance to adjacent vessels. (**C**) Local recurrence regarding the possible influence of the distance to the bronchus.

100×10^9/L. Clinical history that revealed former thoracic surgical interventions was not an exclusion criterion and was shown in 18 patients (22.5%).

All patients provided written informed consent of the ablation therapy and its possible complications. We had an IRB approval for the retrospective study design.

Interventional procedure

Percutaneous radiofrequency ablation (PRFA) was performed under image guidance by using a 16- and 64-row CT scanner (Toshiba Aquilon 16, Toshiba Prime 64, Japan). Ablation energy was produced by an RF-generator (RF3000®, Boston Scientific, USA) with a maximum power of 200 W and transmitted by impedance-based expandable needle electrodes (LeVeen®, Boston Scientific, Nattick, MA). All patients underwent intravenous sedation with Midazolam and Fentanyl on demand and local anesthesia with Xylocain.

Under CT guidance, a suitable positioning of the patient according to an optimal skin entry site was chosen, allowing the shortest and safest path to reach the target lesion without affecting endangered anatomic structures such as pleura, blood vessels or bronchial tubes. The needle electrode was inserted under conditions of cutaneous sterility. After correct placement of the needle electrode in the tumor, the RF-ablation procedure was started under step-wise settings following different algorithms depending on the localization of the tumor and according to pleural distance. After roll-off in impedance-control mode, ablation was performed in a second cycle with energy lowered to a 70%-level compared to former maximal power output. The defined ablation area always encompassed a standard 0.5 cm safety margin to avoid residual local tumor progression. Following the thermal ablation procedure, the needle electrode was pulled back under track ablation with an energy of 10 W to destroy possible transmitted tumor

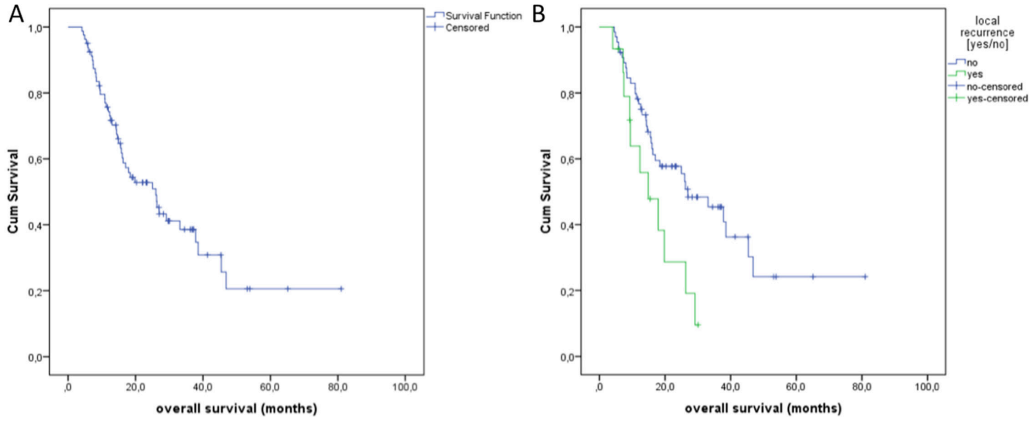

Figure 4: (**A)** Overall Survival (OS) of all treated primary and secondary pulmonary lesions with a median of 27 months. (**B)** OS depending on the local recurrence.

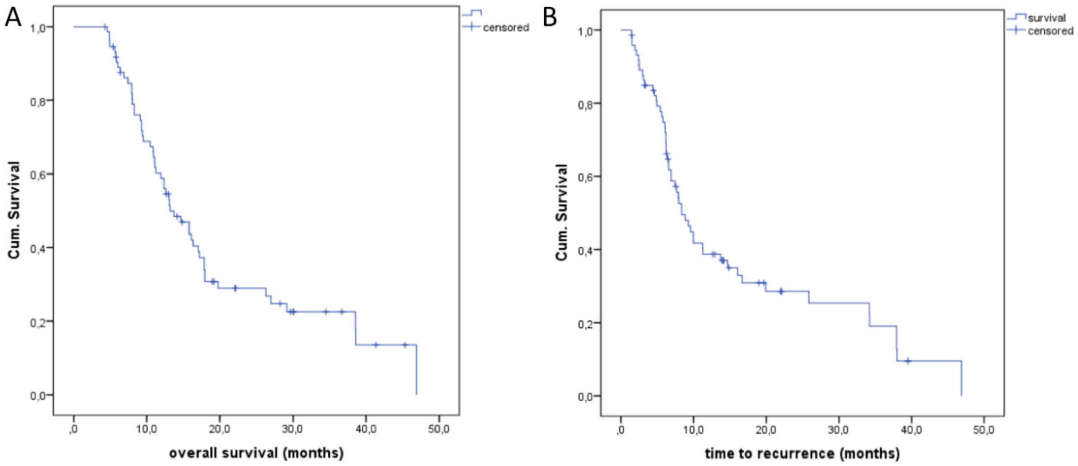

Figure 5: (**A**) Overall Survival (OS) of the colorectal lung metastases with a median of 13 months. (**B)** Time to recurrence (TTR) of lung metastases of colorectal cancer with a median of 8 months.

cells along the pass channel and to prevent pleural bleeding complications.

To conclude the procedure, a CT scan of the ablation area was performed upon request to assure technical success and to rule out early complications. After treatment, patients were kept under clinical observation to monitor their general and cardiorespiratory condition. To follow the possible evolution of complications such as pneumothorax, chest X-rays were obtained at 4 hours and 24 hours after intervention in all cases.

Assessment of outcome variables

The primary endpoint of our study was local tumor control (LTC). Secondary endpoints were technical success and safety as well as overall survival (OS). Technical success here refers to the correct placement of the needle electrode and procedural settings fulfilling the standard ablation protocol.

Follow-up visits coincided with a baseline CT scan within 1 month after RFA treatment, a CT scan every three months following and a final CT scan as control (Figure 6A–6C). We included patients with a minimum of two follow-up CT scans. Because the RFA causes a coagulation necrosis in the ablation zone presented as a high density area in CT, the follow-up CT scans were compared with the baseline scan shortly taken after the ablation to exclude a false positive tumor progression. Treatment evaluation, i.e. changes of the high density surrounding area or tumor sizes were analyzed by using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [30], according to the follow-up scheme of the RAPTURE study [5]. Two

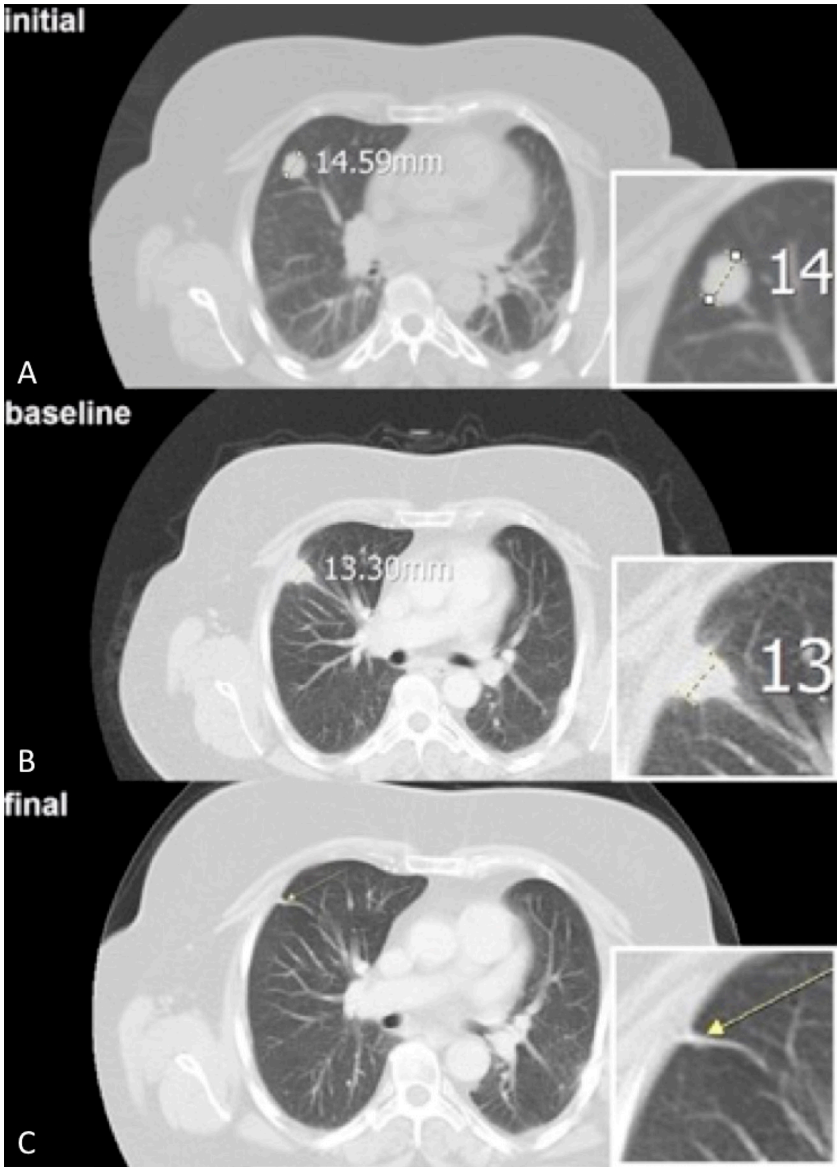

Figure 6: (**A)** The axial initial CT scan of the right lung shows a 1.5 cm large tumor of a patient with a colorectal cancer metastasis. (**B)** After the CT-guided radiofrequency ablation (RFA) of the pulmonary lesion, the baseline CT scan shows a typical surrounding pleural reaction. (**C**) Complete remission (CR) after a follow-up period of 25 months.

Table 1: Median overall survival, local recurrence, local tumor control and the influence of possible predictive factors

Total number of patients (*n*)	**79**
Number of lesions (*n*)	**129**
Median follow up (mo.)	**14**
Median overall survival (OS, mo.)	**27**
Median OS regarding tumor size:	
0.5–1 cm	**26.2**
1–2 cm	**26.0**
2–3 cm	**16.3**
Local tumor control (*n*; %)	**110; 85.3**
complete remission (CR)	**34; 26.4**
partial remission (PR)	**48; 37.2**
stable disease (SD)	**28; 21.7**
progressive disease (PD)	**19; 14.7**
Local recurrence (*n*; %) regarding	
Tumor size	***p* = 0.013**
0.5–1 cm	**7.3**
1–2 cm	**16.2**
2–3 cm	**28.6**
Distance to pleura	***p* = 0.807**
< 1cm	**2**
≥ 1cm	**17**
Distance to vessel	***p* = 0.812**
0–5 mm	**2**
5–20 mm	**12**
> 20 mm	**5**
Distance to bronchi	***p* = 0.822**
0–5 mm	**2**
5–20 mm	**10**
> 20 mm	**7**
Subanalyze of colorectal cancer metastases:	
Median overall survival (OS)	**13**
Median time to recurrence (TTR)	**8**

Subanalyze of colorectal cancer metastases

independent radiologists with 7 and 13 years' experience in oncological/interventional radiology evaluated the CT scans. In cases of discordance, results were obtained by consensus. Based on CT analysis, LTC was evaluated by axial lesion size measurement in longest diameter, lesion geometry and lesion enhancement using *Infinitt PACS*® as the established software for radiological analysis and picture diagnostics. Target tumors, showing at least a 30% decrease in longest diameter compared with the diameter measured at baseline CT, no evidence of tumor growth and no evidence of contrast enhancement, were assumed to have undergone partial and complete remission (PR, CR). Target tumors seen in follow-ups that showed evidence of an increase in longest diameter of at least a 20% tumor growth, or intratumoral contrast uptake, were assumed to have a progressive disease (PD) as a consequence of an incomplete ablation.

Potential complications during or after the procedure were monitored and reported. Safety assessment dealing with procedure-related complications were divided into *major* and *minor* complications. Major complications were pneumothorax and pleural effusion that required chest tube placement; in general terms, major complications limited the patient's general condition and especially restricted lung function to a certain extent, making repeated treatment necessary. Minor complications appeared less dangerous, self-limiting and tolerable, so the patient only required observation without the need of intervention. We analyzed

Table 2: Adverse events after the treatment of primary and secondary lung malignancies with CT-guided radiofrequency ablation

Number of adverse events (*n*)	23
pneumothorax (*n*; %)	19; 147%
pleural effusion (*n*; %)	2; 1.6%
skin burning (*n*; %)	1; 0.8%
infection/abscess (*n*; %)	1; 0.8%
Number of *major* events (*n*, %)	**5; 3.9%**
Number of *minor* events (*n*, %)	**18; 14.0%**

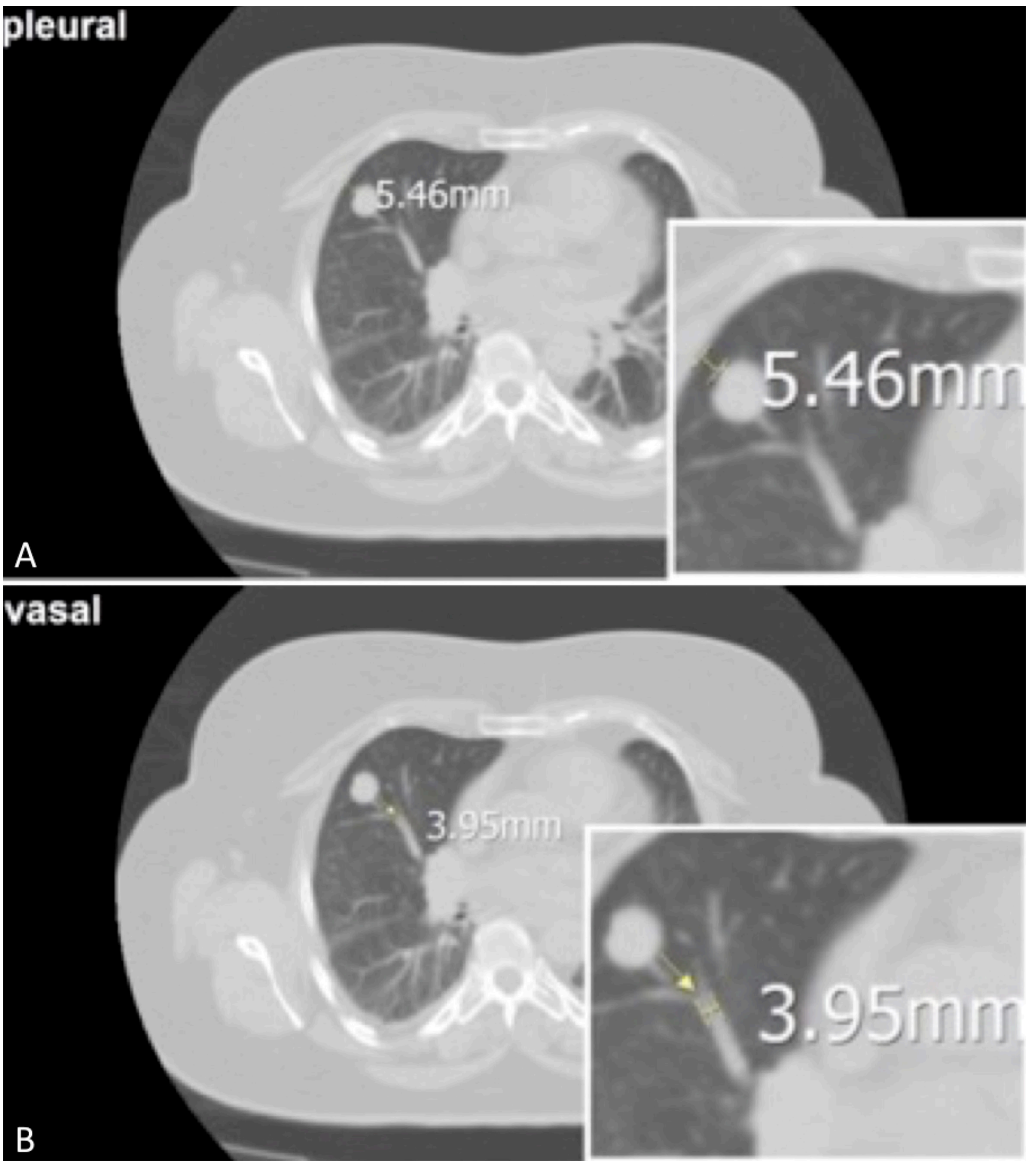

Figure 7: (**A**) The axial CT scan of a pulmonary lesion shows the distance to the pleura (5 mm) as a possible influence. (**B**) and the distance to an adjacent vessel (4 mm).

Table 3: Moderate and severe adverse events (Grade II and III) after RF ablation of pulmonary lesions rated with CTCAE (Common terminology criteria for adverse events)

CTCAE Grade:	II	III	IV	V
Pneumothorax	1	0	0	0
Pleural effusion	0	2	0	0
Skin Burning	0	1	0	0
Pulmonary infection	1	0	0	0

Table 4: Clinical characteristics of patients with primary and secondary pulmonary lesion

Total number of patients (*n*)	**79**
Sex (m; w)	m = 47; w = 32
Median age (y), range	(65.1; 36–83)
Total pulmonary lesions (*n*)	**129**
Histology of Primary tumor	
Colorectal cancer (*n*)	74
Malignant melanoma (*n*)	13
Renal cell carcinoma (*n*)	13
Non-small-cell lung cancer (*n*)	5
Other primary malignancies (*n*)	24
Median size of pulmonary lesions, range (cm)	1.2 cm, (0.5–3.0 cm)
Previous lung surgery (*n*)	18; 22, 5%
Median treatment time (min)	17 (10–30)

the adverse events (AEs) using the "Common Terminology Criteria for Adverse Events Version 3.0" (CTCAE 3.0).

Assessment of predictive factors

In order to identify possible predictive factors co-variating with the success of treatment, we examined the influence of a) initial lesion size, b) distance to vessels, c) bronchi and d) pleura (Figure 7A). We defined the distance of a pulmonary lesions to the next measurable vessel (Figure 7B) or bronchus (0–0.5 cm; 0.5–2 cm; > 2 cm). We also evaluated e) the vessel and f) bronchial caliber both contributing to the local 'heat sink effect'.

Statistical methods

Our data was collected from our internally established data base ASENA® (LoeScap Technology GmbH) and tabulated in a Microsoft Excel® 2007 (MS Windows®) worksheet. Statistical analysis was performed using SPSS® 21 (MS Windows®). The Kaplan-Meier method was used to estimate survival functions. Median survival estimates were reported with 95% confidence intervals. Comparisons of survival functions were performed by using both the log-rank test and the Breslow test. Correlations between the variables were comprehensively analyzed by means of Cox regressions. $P < 0.05$ was considered to indicate statistically significant difference.

CONFLICTS OF INTEREST

None.

REFERENCES

1. Fry WA, Phillips JL, Menck HR. Ten-year survey of lung cancer treatment and survival in hospitals in the United States: a national cancer data base report. Cancer. 1999; 86:1867–76.
2. Hoffman PC, Mauer AM, Vokes EE. Lung cancer. Lancet. 2000; 355:479–85.
3. Pagès PB, Seraysson C, Brioude G, Falcoz PE, Brouchet L, Le Pimpec-Barthes F, Thomas PA, Bernard A. Risk factors for survival and recurrence after lung metastasectomy. J Surg Res. 2016; 203:293–300.
4. Vogl TJ, Naguib NN, Lehnert T, Nour-Eldin NE. Radiofrequency, microwave and laser ablation of pulmonary neoplasms: clinical studies and technical considerations—review article. Eur J Radiol. 2011; 77:346–57.

5. Lencioni R, Crocetti L, Cioni R, Suh R, Glenn D, Regge D, Helmberger T, Gillams AR, Frilling A, Ambrogi M, Bartolozzi C, Mussi A. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). Lancet Oncol. 2008; 9:621–28.

6. Simon CJ, Dupuy DE, DiPetrillo TA, Safran HP, Grieco CA, Ng T, Mayo-Smith WW. Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. Radiology. 2007; 243:268–75.

7. Garetto I, Busso M, Sardo D, Filippini C, Solitro F, Grognardi ML, Veltri A. Radiofrequency ablation of thoracic tumours: lessons learned with ablation of 100 lesions. Radiol Med (Torino). 2014; 119:33–40. https://doi.org/10.1007/s11547-013-0308-5.

8. Liu Z, Ahmed M, Weinstein Y, Yi M, Mahajan RL, Goldberg SN. Characterization of the RF ablation-induced 'oven effect': the importance of background tissue thermal conductivity on tissue heating. Int J Hyperthermia. 2006; 22:327–42.

9. Lu DS, Raman SS, Vodopich DJ, Wang M, Sayre J, Lassman C. Effect of vessel size on creation of hepatic radiofrequency lesions in pigs: assessment of the "heat sink" effect. AJR Am J Roentgenol. 2002; 178:47–51.

10. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, Fowler J, Gore E, Choy H. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010; 303:1070–76.

11. Vahdat S, Oermann EK, Collins SP, Yu X, Abedalthagafi M, Debrito P, Suy S, Yousefi S, Gutierrez CJ, Chang T, Banovac F, Anderson ED, Esposito G, Collins BT. CyberKnife radiosurgery for inoperable stage IA non-small cell lung cancer: 18F-fluorodeoxyglucose positron emission tomography/computed tomography serial tumor response assessment. J Hematol Oncol. 2010; 3:6.

12. Dupuy DE. Image-guided thermal ablation of lung malignancies. Radiology. 2011; 260:633–55.

13. Zhao Q, Tian G, Chen F, Zhong L, Jiang T. CT-guided percutaneous laser ablation of metastatic lung cancer: three cases report and literature review. Oncotarget. 2017; 8:2187–96. https://doi.org/10.18632/oncotarget.13901.

14. Nour-Eldin NA, Exner S, Al-Subhi M, Naguib NN, Kaltenbach B, Roman A, Vogl TJ. Ablation therapy of non-colorectal cancer lung metastases: retrospective analysis of tumour response post-laser-induced interstitial thermotherapy (LITT), radiofrequency ablation (RFA) and microwave ablation (MWA). Int J Hyperthermia. 2017; 33:820–29.

15. Yamakado K, Hase S, Matsuoka T, Tanigawa N, Nakatsuka A, Takaki H, Takao M, Inoue Y, Kanazawa S, Inoue Y, Sawada S, Kusunoki M, Takeda K. Radiofrequency ablation for the treatment of unresectable lung metastases in patients with colorectal cancer: a multicenter study in Japan. J Vasc Interv Radiol. 2007; 18:393–98.

16. de Baère T, Aupérin A, Deschamps F, Chevallier P, Gaubert Y, Boige V, Fonck M, Escudier B, Palussiére J. Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases. Ann Oncol. 2015; 26:987–91.

17. Iida T, Nomori H, Shiba M, Nakajima J, Okumura S, Horio H, Matsuguma H, Ikeda N, Yoshino I, Ozeki Y, Takagi K, Goya T, Kawamura M, et al, and Metastatic Lung Tumor Study Group of Japan. Prognostic factors after pulmonary metastasectomy for colorectal cancer and rationale for determining surgical indications: a retrospective analysis. Ann Surg. 2013; 257:1059–64.

18. Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol. 2013; 20:572–79.

19. Schneider T, Reuss D, Warth A, Schnabel PA, von Deimling A, Herth FJ, Dienemann H, Hoffmann H. The efficacy of bipolar and multipolar radiofrequency ablation of lung neoplasms - results of an ablate and resect study. Eur J Cardiothorac Surg. 2011; 39:968–73.

20. Hiraki T, Sakurai J, Tsuda T, Gobara H, Sano Y, Mukai T, Hase S, Iguchi T, Fujiwara H, Date H, Kanazawa S. Risk factors for local progression after percutaneous radiofrequency ablation of lung tumors: evaluation based on a preliminary review of 342 tumors. Cancer. 2006; 107:2873–80.

21. Hiraki T, Gobara H, Fujiwara H, Ishii H, Tomita K, Uka M, Makimoto S, Kanazawa S. Lung cancer ablation: complications. Semin Intervent Radiol. 2013; 30:169–75.

22. Zhu JC, Yan TD, Morris DL. A systematic review of radiofrequency ablation for lung tumors. Ann Surg Oncol. 2008; 15:1765–74.

23. Carrafiello G, Mangini M, Fontana F, Di Massa A, Ierardi AM, Cotta E, Piacentino F, Nocchi Cardim L, Pellegrino C, Fugazzola C. Complications of microwave and radiofrequency lung ablation: personal experience and review of the literature. Radiol Med (Torino). 2012; 117:201–13.

24. Bojarski JD, Dupuy DE, Mayo-Smith WW. CT imaging findings of pulmonary neoplasms after treatment with radiofrequency ablation: results in 32 tumors. AJR Am J Roentgenol. 2005; 185:466–71.

25. Hiraki T, Mimura H, Gobara H, Sano Y, Fujiwara H, Iguchi T, Sakurai J, Kishi R, Kanazawa S. Two cases of needle-tract seeding after percutaneous radiofrequency ablation for lung cancer. J Vasc Interv Radiol. 2009; 20: 415–418.

26. Gobara H, Arai Y, Kobayashi T, Yamakado K, Inaba Y, Kodama Y, Yamagami T, Sone M, Watanabe H, Okumura Y, Shinya T, Kurihara H, Kanazawa S. Percutaneous radiofrequency ablation for patients with malignant lung tumors: a phase II prospective multicenter study (JIVROSG-0702). Jpn J Radiol. 2016; 34:556–63.

27. Higuchi M, Honjo H, Shigihara T, Shishido F, Suzuki H, Gotoh M. A phase II study of radiofrequency ablation

therapy for thoracic malignancies with evaluation by FDG-PET. J Cancer Res Clin Oncol. 2014; 140:1957–63.

28. Bonichon F, Palussiere J, Godbert Y, Pulido M, Descat E, Devillers A, Meunier C, Leboulleux S, de Baere T, Galy-Lacour C, Lagoarde-Segot L, Cazeau AL. Diagnostic accuracy of 18F-FDG PET/CT for assessing response to radiofrequency ablation treatment in lung metastases: a multicenter prospective study. Eur J Nucl Mol Imaging. 2013; 40:1817–27.

29. de Baere T, Tselikas L, Gravel G, Deschamps F. Lung ablation: best practice/results/response assessment/role alongside other ablative therapies. Clin Radiol. 2017; 72:657–64.

30. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228–47.

Veröffentlichung 10

Image-guided Interstitial Brachytherapy in the Management of Metastasized Anal Squamous Cell Carcinoma.

Heinze C, Omari J, Othmer M, Hass P, Seidensticker M, **Damm R**, Ricke J, Pech M, Powerski MJ.

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Image-guided Interstitial Brachytherapy in the Management of Metastasized Anal Squamous Cell Carcinoma

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Abstract. *Background/Aim: Interstitial brachytherapy (IBT) has been shown to provide high tumor control rates in metastatic colorectal carcinoma. Our aim was to evaluate efficacy and safety of IBT in patients with metastatic anal squamous cell carcinoma (mASCC). Patients and Methods: Seven patients with a total of 38 unresectable ASCC metastases (28 liver, nine lung, one nodal metastases) were treated with computed tomographic or open magnetic resonance imaging-guided IBT using an iridium-192 source. Clinical and image-based follow-up were performed every 3 months after treatment. Results: Local tumor control rate was 97.4% during a median follow-up of 15.2 months. Median progression-free survival was 3.3 months (range=2.5-32.6 months). Median overall survival after IBT was 25.2 months (range=6.5-51.0 months). No severe adverse events (grade 3 or more) were recorded. Conclusion: Image-guided IBT is a safe and particularly effective treatment in patients with mASCC and might provide a well-tolerated therapeutic option in a multidisciplinary setting.*

Squamous cell cancer is the dominant histological type in cancer of the anal canal; it is a rather rare malignancy with approximately 27,000 new cases worldwide in 2008, although the incidence is constantly rising (1, 2). In around 70-90% of cases it is associated with human papilloma virus infection, and immunosuppression is another risk factor of great significance, accounting for an elevated incidence rate in HIV-infected individuals (3, 4). Five-year overall survival (OS) was reported as 44-78% (5). Definitive chemoradiation is the standard organ-preserving treatment for localized ASCC (6); after locoregional recurrence, abdominoperineal resection remains the only salvage option. Moreover, about 20% of patients develop distant metastases after curative treatment (7). After metastatic relapse, the prognosis is poor, with a 5-year survival rate of 18% and median OS of 8-15 months, reported in small case studies (7-10). Guidelines from the European Society for Medical Oncology (ESMO) state that there is currently no consensus on a standard treatment algorithm considering chemotherapy in advanced or metastatic disease (mASCC); however, in the case of isolated metastatic volume, *i.e.* oligometastatic disease, surgical resection is a considerable option (5). Yet, in most cases resection is not possible due to the distribution or volume of the lesions, or due to contraindications for surgery or general anesthesia, apart from associated morbidity and mortality. Aside from surgery, a multidisciplinary approach to localized therapy of mASCC might also include image-guided local ablation techniques such as radiofrequency ablation (RFA) or interstitial brachytherapy (IBT). Percutaneous IBT of parenchymal organs is a relatively new technique that is adapted from conventional high-dose-rate brachytherapy (11). In IBT an iridium-192 source is temporarily introduced into metastatic lesions *via* percutaneously implanted applicators, which are placed under imaging guidance in a minimal invasive intervention, thereby enabling a clearly delineated single-fraction irradiation of the target volume. IBT has already been shown to be an efficient, yet gentle treatment with a minimum of complications in ablation of primary or secondary malignancies at various sites, *e.g.* colorectal cancer and hepatocellular carcinoma (12-14). To our knowledge, no data have been published, so far, evaluating the efficacy of IBT in the treatment of mASCC. In this study, safety and efficacy were retrospectively analyzed in a cohort of patients with unresectable ASCC metastases who underwent image-guided IBT.

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Key Words: Anal cancer, metastases, interventional oncology, image-guided intervention, interstitial brachytherapy.

Table I. *Characteristics of the patient population and the treated metastases. Prior to interstitial brachytherapy (IBT) all patients received irradiation of the primary tumor; patient 3 refused chemotherapy.*

Patient	Gender	Age, years	Distant metastasis	Chemotherapy before IBT	Localization of target lesion	Number of lesions	Maximum diameter of target lesion (cm)	D100 Administered (Gy)	Local recurrence (months after IBT)
1	F	60	Synchronous	Cisplatin, 5-FU, mitomycin	Liver, lung	5	0.6-4.0	21.3-32.6	-
2	F	77	Metachronous	FU, mitomycin	Lymph node	1	1.4	21.1	-
3	F	46	Synchronous	-	Liver, lung	15	0.4-2.9	14.7-21.0	-
4	F	51	Synchronous	Cisplatin, 5-FU, folinic acid	Liver	6	1.0-4.0	14.6-16.2	-
5	M	66	Synchronous	Cisplatin, 5-FU	Liver	1	6.2	17.1	-
6	M	67	Metachronous	Cisplatin, 5-FU	Lung	1	2.1	24.0	7.6
7	F	74	Metachronous	Cisplatin, 5-FU, folinic acid, mitomycin	Liver	9	0.9-1.7	15.0-17.3	-

F: Female; 5-FU: 5-fluorouracil; M: male.

Patients and Methods

Eligibility criteria and patients. Inclusion criteria were: (a) technically unresectable metastases of the anal canal, (b) medical contraindication for resection or severe comorbidities, (c) refusal of surgery, (d) East Coast Oncology Group (ECOG) performance status below 2, (e) appropriate liver parameters (bilirubin <30 μmol/l) and sufficient lung capacity (FEV1 >1.5 l) in the case of ablation of hepatic and pulmonary metastases, respectively. No upper limit was placed upon maximum tumor diameter or number of lesions. Contraindications to local ablation were (a) peritoneal carcinomatosis; (b) prognosis limiting, widespread systemic disease; (c) uncorrectable coagulation defects (target values: platelet count>50,000/nl, international normalized ratio >1.5, partial thromboplastin time <50 s); (d) lack of consent. In consideration of these criteria, 7 patients (five female; median age=66 years range=46-77 years) were included with 38 inoperable metastases. Patient recruitment was blinded and carried out between December 2008 and June 2016. All patients were diagnosed with histologically proven ASCC and displayed tumor progression at the time of referral to our clinic; every case was discussed in an interdisciplinary tumor conference, where the indication for IBT was determined.

Prior to ablation, six patients were treated with concurrent chemoradiation, patient 3 only received radiotherapy of the primary tumor due to refusal of chemotherapy. Patient 6 was treated with abdominoperineal resection after local recurrence. Furthermore, prior to IBT, patient 4 underwent radioembolization of the liver and patient 5 underwent hemihepatectomy (for detailed patient characteristics see Table I). All patients underwent a full evaluation of their clinical status with a physical examination and laboratory assessment. Furthermore, whole-body contrast-enhanced computed tomography (CT) and a gadolinium (Gd)-enhanced magnetic resonance imaging (MRI) (Primovist®, Bayer, Pharma, Leverkusen, Germany) was performed to acquire complete staging. All patients undergoing IBT of lung lesions had a clinically fully compensated lung function. Approval of the Ethics Committee for the analysis of the patient data was obtained (EudraCT-No 2011-003220-12).

Interventional technique and irradiation. The applied technique has been described elsewhere in detail (13, 15, 16). Under guidance of a fluoroscopy-CT (Toshiba, Aquilion, Japan) or real-time MRI using a 1.0-T open MRI scanner (Panorama HFO; Philips Healthcare, Best, the Netherlands) an 18-gauge needle was introduced into the target lesion. A flexible 6-F catheter sheath (Terumo Radifocus® Introducer II, Terumo Europe, Leuven, Belgien) was inserted over a stiff angiography guide wire using Seldinger's technique followed by the placement of a 6-F afterloading catheter (Afterloadingkatheter; Primed® Medizintechnik GmbH, Halberstadt, Germany). The intervention was performed under local anesthesia (lidocaine) and analgo-sedation (midazolam and fentanyl). The number and arrangement of the catheters was determined by the shape, size and location of the target lesion. After catheter positioning, a contrast-enhanced CT scan in breath-holding technique or a gadolinium-based MRI scan was obtained to document correct catheter positioning and for irradiation planning. On these images, the target volume was drawn precisely as gross tumor volume (GTV) and clinical target volume (CTV), additionally, organs at risk (OARs; *e.g.* stomach, duodenum) were marked by the interventional radiologist and the radiooncologist. Dose calculation was performed using the acquired dataset with Oncentra-Masterplan (Oncentra® Brachy treatment planning system; Elekta AB, Stockholm, Sweden). The calculated isodose lines, relative to margins of the CTV, were controlled and adapted slice by slice. All irradiations were administered as single-fraction irradiations using an iridium-192 source with a nominal activity of 10 Ci. A reference dose of 20 Gy was prescribed to our patients, which was defined as the minimum dose enclosing the complete CTV (D100). Higher doses inside the tumor volume were permitted and not limited. Depending on adjacent OARs, dose limitations were taken into account, *i.e.* gastric or duodenal wall (<15 Gy/ml). After irradiation the catheters were removed and the puncture channels were sealed using gelfoam or fibrin tissue glue. Figure 1 illustrates the interventional technique.

Follow-up. After IBT, every 3 months clinical, laboratory and imaging follow-up (contrast-enhanced whole-body CT and Gb-EOB-DTPA-enhanced MRI of the liver) were performed. Local tumor control (LTC) and progression-free survival (PFS) were assessed by employing RECIST criteria (RECIST version1.1.) (17), OS was calculated from the date of ablation to death. Adverse events were defined according to Common Terminology Criteria for Adverse Events (CTCAE version 4.03) (18).

Study design and statistical analysis. Primary endpoints were LTC and safety; secondary endpoints were OS and PFS. The results were analyzed in a non-randomized and retrospective approach. LTC, OS and PFS were evaluated employing the Kaplan–Meier method with SPSS (Version 22.0; IBM Corp, Armonk, NY, USA). Safety was evaluated descriptively.

Results

The median diameter of the target lesions was 1.2 cm (range=0.4-6.2 cm). Due to size and location of the GTV, 14 liver lesions were treated under MRI guidance (maximum diameter range=0.4-3.2 cm), the remaining 24 lesions were visualized with CT. A total of 28 liver lesions, nine lung metastases and one lymph-node metastasis were treated. All 38 lesions were irradiated in a total of 12 sessions: in three patients, local ablation was completed after one session, three patients underwent two sessions due to progressive disease after 12.8, 2.5 and 2.6 months, respectively. The treatment of patient 3 was split into three sessions due to progression 5.6 months after the first IBT. The median hospital stay was 5 days (range=3-10 days); patient 2 stayed 10 days due to evaluation-angiography prior to radioembolization of liver metastases in the same hospital stay. We report four cases of pneumothorax: three required a chest drain (classified as grade 2 adverse event, according to CTCAE 4.03), and one regressed spontaneously. In two patients, we recorded an increased level of systemic inflammation markers (C-reactive protein, and leukocytosis) without fever or additional symptoms; one was treated with *i.v.* antibiotics (ciproflaxacin and metronidazole) leading to a rapid normalization. Two patients reported unspecific nausea. No severe adverse events (grade 3 or more) were recorded.

The intended minimum tumor dose (D100) was 20 Gy, although the radiotherapy dose had to be lowered in the case of radiation in the vicinity of an OAR and in the case of several liver lesions in order to preserve liver function (at least 33% of the liver parenchyma should not be irradiated with more than 5 Gy) (12). The median administered D100 was 16.2 Gy (range=12.0-32.6 Gy). During the treatment, no adjacent OARs were irradiated in excess of the critical value. The median irradiation time was 30.5 min (range=10-40 min). The median follow-up time was 15.2 months (range=2.5-32.6 months). One patient exhibited local recurrence at the GTV 7.6 months after IBT, resulting in an LTC rate of 97.4% in the Kaplan–Meier analysis (Figure 2). The recurrent lesion was a lung lesion covered with a minimum tumor dose of 24 Gy at time of treatment.

PFS ranged from 2.5-32.6 months, with a median of 3.3 months (Figure 3). Patient 5 was excluded from the PFS analysis due to lack of detailed information regarding the time point of disease progression. Within the follow-up period, all patients had systemic progressive disease. In the time between local ablation and systemic progression, four patients received specific tumor therapy, in detail: palliative re-radiation of the recurrent primary tumor, radioembolization of the liver, palliative chemotherapy, and surgical resection plus irradiation of a cerebellar metastasis, respectively. At the date of censoring, one patient of the analyzed population was still alive (patient 1 received treatment in October 2015 and January 2017). The median OS of the remaining patients was 25.2 months (range=6.5-51.0 months) (Figure 4). Survival after recurrence ranged from 3.2 to 32.6 months, with a median of 18.3 months.

Discussion

Since cancer of the anal canal is a rather rare malignancy with a likelihood of up to 20% for distant metastases after curative treatment data regarding management of mASCC is scarce. Hence, according to the ESMO guidelines a recommendation cannot be made for a specific palliative chemotherapeutic algorithm in advanced/mASCC. The reported 5-year survival rate remains poor at approximately 18% (7, 8). The existing treatment regimens are extrapolated from those used for SCC of the lung or the cervix and based on case studies or series. Nevertheless, the ESMO guidelines state that fit patients with symptomatic metastatic or recurrent disease not amenable to surgery should be considered for chemotherapy, usually with a combination of cisplatin and 5-fluoruracil, which is a well-documented regimen, for instance with a reported median OS of 34.5 months in a case series of 18 patients (5, 19). Response is also reported for carboplatin, doxorubicin, taxanes and irinotecan with/without cetuximab or the combinations of these agents but these regimens are less evaluated (20). Furthermore, possible subsequent therapy concerning immune checkpoint inhibition was recently assessed in heavily pretreated patients with metastatic disease or locally advanced recurrent disease: 37 patients were enrolled in a single-arm, phase 2 trial with nivolumab, with a reported median PFS of 4.1 months and a median OS of 11.5 months (21).

In metastatic colorectal cancer, resection of liver metastases has proven to be curative, with 5-year OS rates of 16-74% (median=38%) (22), although data regarding surgical resection of ASCC metastases are limited. To our knowledge, there is no study evaluating the outcome of an ASCC population after surgery, however, there are two studies investigating the outcome of patients with SCC of any primary site after resection of liver metastases: Omich *et al*. found a cumulative median OS of 33.3 months and a median PFS of 9.3 months in 28 patients (19 with ASCC) (23); Pawlik *et al*. reported a cumulative median OS of 22.3 months and a median PFS of 9.8 months (27/52 diagnosed with ASCC) (24). However, in general, surgical resection is applicable to a limited number of cases in metastatic disease, for instance, in metastatic colorectal cancer, curative resection of liver metastases is not

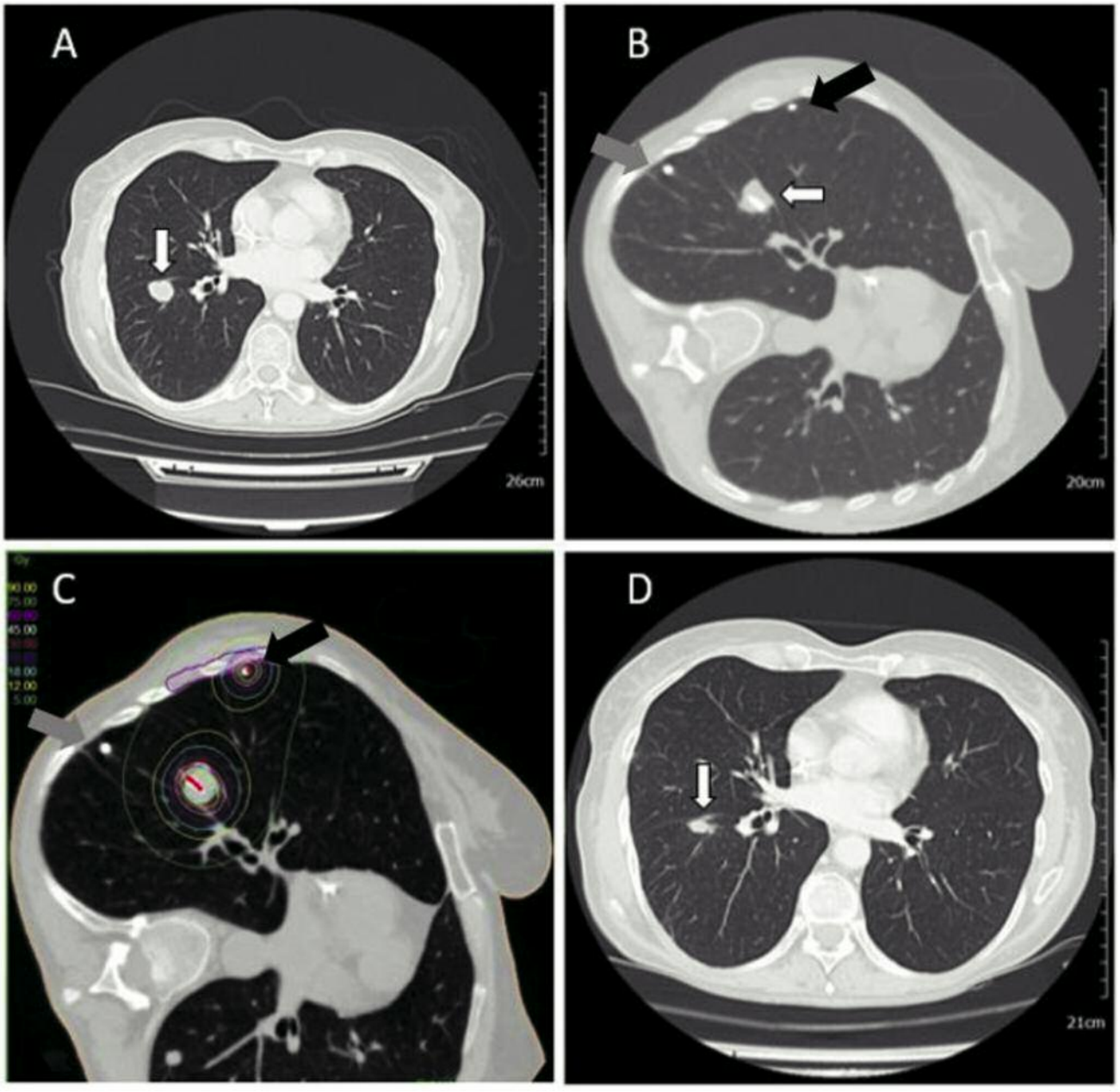

Figure 1. *Interventional technique and local tumor control in patient 1 with metastatic anal squamous cell carcinoma (ASCC). A: Pre-interventional contrast-enhanced computed tomographic (CT) slice showing a metastasis of ASCC (white arrow) in the lower lobe of the right lung. The second clinical target volume (CTV) is not depicted in this slice. B: CTV in the lower lobe with one percutaneously implanted brachytherapy catheter (white arrow). A second CTV was located subpleurally in the upper lobe of the right lung (black arrow). C: Planning CT with CTV indicated (red line), catheter (marked in red) and isodose lines for both CTVs in the lower and middle lobe (black arrow). D: Contrast-enhanced CT slice 3 months after interstitial brachytherapy showing partial remission of the treated lesion in the lower lobe (white arrow). The second CTV is not depicted in this slice. Gray arrows: Chest drain.*

possible in approximately 80% of cases (25). Furthermore, liver resection in particular is associated with significant morbidity and mortality, with regard to the extent of resection and the remaining functional liver tissue.

In contrast, image-guided interstitial IBT provides a safe and minimally invasive approach. According to the literature, grade 3-4 adverse events, *i.e.* bleeding, requiring angiographic embolization, occurs in up to 3% (15, 26). In

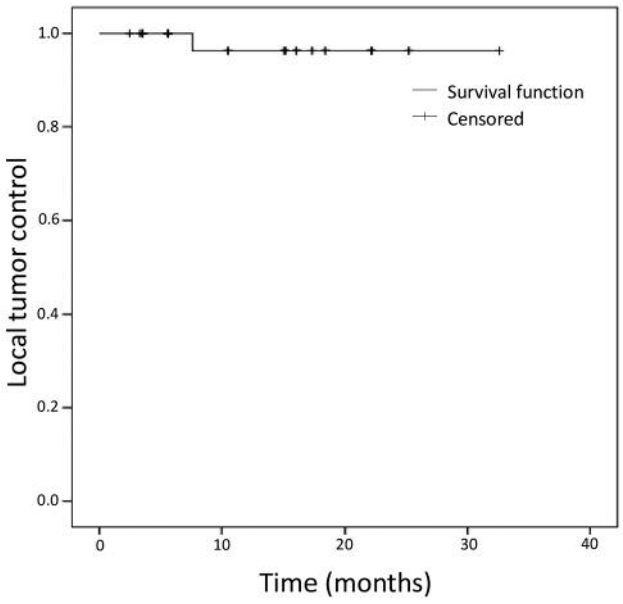

Figure 2. *Kaplan–Meier curve for local tumor control after interstitial brachytherapy.*

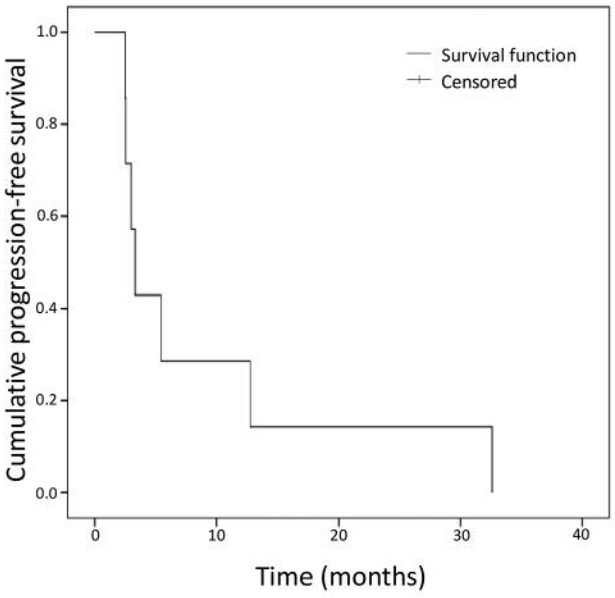

Figure 3. *Kaplan–Meier curve for progression-free survival after interstitial brachytherapy.*

the study herein, we did not report any severe adverse event (grade 3 or more). The median hospital stay was 5 days (range=3-10 days). In general, patients tolerated the treatment well and could have been discharged earlier, but due to the risk of occult bleeding, observation of at least 48 h after ablation was considered necessary.

IBT has primarily been evaluated in primary and secondary liver malignancies, such as hepatocellular carcinoma and particularly in metastatic colorectal cancer, demonstrating LTC rates of 95% and 88.3% after 12 months, respectively. Furthermore, this novel technique has also been shown to provide favorable LTC rates in the ablation of retroperitoneal lesions with LTC rates up to 88% 12 months post IBT (12-14). Corresponding with these findings, in the study herein we report an excellent LTC of 97.4% over a median follow-up of 15.2 months. Referring to the existing literature, numerous studies evaluating the effect and outcome of radiotherapy of the primary tumor are available, however, to our knowledge there are no studies assessing the efficacy of stereotactic body radiation nor of local ablation (*i.e.* RFA or IBT) in (oligo-)metastatic ASCC. However, few published data exist regarding the advantage of an aggressive multidisciplinary treatment (MDT) in an oligometastatic setting: Eng and colleagues evaluated outcomes among 77 patients who received systemic chemotherapy or chemotherapy plus MDT (33 in the MDT group), *i.e.* surgery (16/33), chemoradiation (14/33) and percutanous RFA (3/33). The MDT group had significantly better median PFS of 16 months and median OS

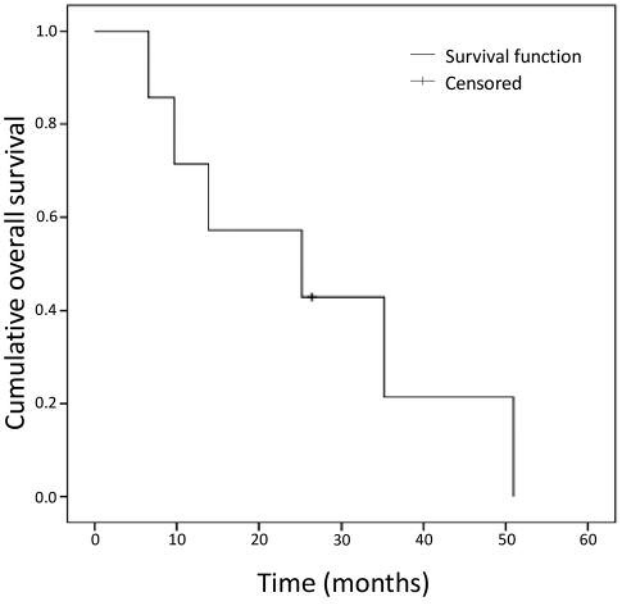

Figure 4. *Kaplan–Meier curve for overall survival of six patients treated with interstitial brachytherapy. At the date of censoring, patient 1 was still alive.*

of 53 months compared to the median PFS and OS of all patients of 7 and 22 months, respectively (27). All patients were treatment-naive for metastatic disease. Similarly, Evesque *et al*. split 50 individuals into a chemotherapy group

and a chemotherapy plus MDT group (30 patients: 13 surgery, 11 radiotherapy, six RFA). Median OS in the MDT group was 22 *versus* 13 months in the chemotherapy group and median PFS was 10 *versus* 5 months (28).

In the herein study, we report an inferior median PFS of 3.3 months (range=2.5-32.6 months), possibly based on the fact that we analyzed a small patient population and, additionally, these selected patients were not naïve for metastatic treatment, six out of seven patients showed failure of palliative chemotherapy (one patient refused chemotherapy). We report a median OS of 25.2 months, ranging from 6.5 to 51 months, providing comparable results to the MDT group of Evesque *et al*. Moreover, we report two long-term survivors: patient 5 with 51 months and patient 7 with 35 months. These findings suggest that highly selected candidates benefit from an aggressive ablative approach even in metastatic disease; furthermore, with knowledge of the survival advantage arising from an assertive MDT approach, IBT provides an additional, well-tolerated and feasible ablative technique in the toolbox against metastatic disease. Furthermore, compared to surgical resection, this method offers advantages in terms of treatment tolerability and accessibility of lesions (in number and location); moreover, compared to RFA as used in the studies mentioned above, IBT is free from technical limitations concerning the potential cooling effect arising from large tumor masses (>5 cm) or from the vicinity to major vessels close to the GTV resulting in a possible incomplete ablation.

However, limitations of this study are its retrospective nature and the low number of patients; furthermore, the treated patient population comprised of selected patients, heavily pretreated in a metastatic setting with a failure of therapeutic strategy. A prospective trial would be needed to identify appropriate candidates, naïve for metastatic treatment, as well as pretreated, and evaluate the outcome after IBT in a multidisciplinary setting. This could possibly establish IBT in the therapeutic algorithm for mASCC, as has already been implemented in the ESMO guidelines for the management of patients with metastatic colorectal cancer (29). However, given the rarity of ASCC, studies concerning the management of patients in an oligometastatic setting are scarce. Our data demonstrate that IBT can be safely and effectively used in the local control of mASCC.

Moreover, referring to the findings of Eng *et al*. and Evesque *et al*., our investigation provides an indication that a more aggressive approach preferably in a multidisciplinary setting might improve the OS of selected patients.

In conclusion, our results confirm that interstitial brachytherapy is a safe and particularly effective therapeutic option in the multidisciplinary management of patients with metastasized squamous cell carcinoma of the anal canal and, moreover, highly selected patients undergoing local treatment might have favorable survival outcomes.

References

1 Islami F, Ferlay J, Lortet-Tieulent J, Bray F and Jemal A: International trends in anal cancer incidence rates. Int J Epidemiol *46*: 924-938, 2017.

2 de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D and Plummer M: Global burden of cancers attributable to infections in 2008: A review and synthetic analysis. Lancet Oncol *13*: 607-615, 2012.

3 Martin D, Balermpas P, Winkelmann R, Rodel F, Rodel C and Fokas E: Anal squamous cell carcinoma-State of the art management and future perspectives. Cancer Treat Rev *65*: 11-21, 2018.

4 Chaturvedi AK, Madeleine MM, Biggar RJ and Engels EA: Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst *101*: 1120-1130, 2009.

5 Glynne-Jones R and Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A and Arnold D: Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up.

6 Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, Peiffert D, van Glabbeke M and Pierart M: Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: Results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol *15*: 2040-2049, 1997.

7 Eng C: Anal cancer: current and future methodology. Cancer Invest *24*: 535-544, 2006.

8 Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM and Daling JR: Anal cancer incidence and survival: The Surveillance, Epidemiology, and End Results experience, 1973–2000. Cancer *101*: 281-288, 2004.

9 Abbas A, Nehme E and Fakih M: Single-agent paclitaxel in advanced anal cancer after failure of cisplatin and 5-fluorouracil chemotherapy. Anticancer Res *31*: 4637-4640, 2011.

10 Jhawer M, Mani S, Lefkopoulou M, Hahn RG, Harris J, Catalano PJ and Haller D: Phase II study of mitomycin-C, adriamycin, cisplatin (MAP) and bIeomycin-CCNU in patients with advanced cancer of the anal canal: An Eastern Cooperative Oncology Group study E7282. Invest New Drugs *24*: 447-454, 2006.

11 Kotsuma T, Yamazaki H, Masui K, Yoshida KEN, Shimizutani K, Akiyama H, Murakami S, Isohashi F, Yoshioka Y, Ogawa K and Tanaka E: Brachytherapy for buccal cancer: from conventional low dose rate (LDR) or mold technique to high dose rate interstitial brachytherapy (HDR-ISBT). Anticancer Res *37*: 6887-6892, 2017.

12 Ricke J, Wust P, Stohlmann A, Beck A, Cho CH, Pech M, Wieners G, Spors B, Werk M, Rosner C, Hanninen EL and Felix R: CT-guided interstitial brachytherapy of liver malignancies alone or in combination with thermal ablation: Phase I-II results of a novel technique. Int J Radiat Oncol Biol Phys *58*: 1496-1505, 2004.

13 Collettini F, Lutter A, Schnapauff D, Hildebrandt B, Puhl G, Denecke T, Wust P and Gebauer B: Unresectable colorectal liver metastases: Percutaneous ablation using CT-guided high-dose-rate brachytherapy (CT-HDBRT). Rofo *186*: 606-612, 2014.

14 Mohnike K, Wieners G, Schwartz F, Seidensticker M, Pech M, Ruehl R, Wust P, Lopez-Hanninen E and Gademann G, Peters N, Berg T, Malfertheiner P and Ricke J: Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: Safety, efficacy, and effect on survival. Int J Radiat Oncol Biol Phys *78*: 172-179, 2010.

15 Bretschneider T, Ricke J, Gebauer B and Streitparth F: Image-guided high-dose-rate brachytherapy of malignancies in various inner organs-technique, indications, and perspectives. J Contemp Brachytherapy *8*: 251-261, 2016.

16 Ricke J and Wust P: Computed tomography-guided brachytherapy for liver cancer. Semin Radiat Oncol *21*: 287-293, 2011.

17 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New Response Evaluation Criteria In Solid Tumours: Revised RECIST guideline (version 1.1). Eur J Cancer *45*: 228-247, 2009.

18 National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) v4.03, 2010. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (last accessed 26 July, 2018).

19 Faivre C, Rougier P, Ducreux M, Mitry E, Lusinchi A, Lasser P, Elias D and Eschwege F: 5-Fluorouracil and cisplatinum combination chemotherapy for metastatic squamous-cell anal cancer. Bull Cancer *86*: 861-865, 1999.

20 Hainsworth JD, Burris Hr, Meluch A, Baker M, Morrissey L and Greco F: Paclitaxel, carboplatin, and long-term continuous infusion of 5-fluorouracil in the treatment of advanced squamous and other selected carcinomas: Results of a Phase II trial. Cancer *92*: 642-649, 2001.

21 Morris VK, Salem ME, Nimeiri H, Iqbal S, Singh P, Ciombor K, Polite B, Deming D, Chan E, Wade JL, Xiao L, Bekaii-Saab T, Vence L, Blando J, Mahvash A, Foo WC, Ohaji C, Pasia M, Bland G, Ohinata A, Rogers J, Mehdizadeh A, Banks K, Lanman R, Wolff RA, Streicher H, Allison J, Sharma P and Eng C: Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): A multicentre, single-arm, phase 2 study. The Lancet Oncology *18*: 446-453, 2017.

22 Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, Alexander DD, Choti MA and Poston G: Survival after liver resection in metastatic colorectal cancer: Review and meta-analysis of prognostic factors. Clin Epidemiol *4*: 283-301, 2012.

23 Omichi K, Mizuno T, Okuno M, Tzeng CD, Conrad C, Chun YS, Aloia TA and Vauthey JN: Long term outcome after resection of liver metastases from squamous cell carcinoma. Eur J Surg Oncol *43*: 2129-2134, 2017.

24 Pawlik TM, Gleisner AL, Bauer TW, Adams RB, Reddy SK, Clary BM, Martin RC, Scoggins CR, Tanabe KK, Michaelson JS, Kooby DA, Staley CA, Schulick RD, Vauthey J-N, Abdalla EK, Curley SA, Choti MA and Elias D: Liver-directed surgery for metastatic squamous cell carcinoma to the liver: Results of a multi-center analysis. Ann Surg Oncol *14*: 2807-2816, 2007.

25 Garden OJ, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, Primrose JN and Parks RW: Guidelines for resection of colorectal cancer liver metastases. Gut *55*: iii1-iii8, 2006.

26 Mohnike K, Neumann K, Hass P, Seidensticker M, Seidensticker R, Pech M, Klose S, Streitparth T, Garlipp B, Benckert C, Wendler JJ, Liehr UB, Schostak M, Goppner D, Gademann G and Ricke J: Radioablation of adrenal gland malignomas with interstitial high-dose-rate brachytherapy: Efficacy and outcome. Strahlenther Onkol *193*: 612-619, 2017.

27 Eng C, Chang GJ, Nancy You Y, Das P, Rodriguez-Bigas M, Xing Y, Vauthey J-N, Rogers JE, Ohinata A, Pathak P, Sethi S, Phillips JK, Crane CH and Wolff RA: The role of systemic chemotherapy and multidisciplinary management in improving the overall survival of patients with metastatic squamous cell carcinoma of the anal canal. Oncotarget *5*: 11133-11142, 2014.

28 Evesque L, Benezery K, Follana P, Tuan Falk A, Doyen J, Reure J, Cavaglione G and François E: Multimodal therapy of squamous cell carcinoma of the anus with distant metastasis: A single-institution experience. Dis Colon Rectum *60*: 785-791, 2017.

29 Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJG, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A and Arnold D: ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol *27*: 1386-1422, 2016.

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Local ablation or radioembolization of colorectal cancer metastases: comorbidities or older age do not affect overall survival.

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RESEARCH ARTICLE Open Access

Local ablation or radioembolization of colorectal cancer metastases: comorbidities or older age do not affect overall survival

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Abstract

Background: Local ablative techniques are emerging in patients with oligometastatic disease from colorectal carcinoma, commonly described as less invasive than surgical methods. This single arm cohort seeks to determine whether such methods are suitable in patients with comorbidities or higher age.

Methods: Two hundred sixty-six patients received radiofrequency ablation (RFA), CT-guided high-dose rate brachytherapy (HDR-BT) or Y90-radioembolization (Y90-RE) during treatment of metastatic colorectal cancer (mCRC). This cohort comprised of patients with heterogenous disease stages from single liver lesions to multiple organ systems involvement commonly following multiple chemotherapy lines. Data was reviewed retrospectively for patient demographics, previous therapies, initial or disease stages at first intervention, comorbidities and mortality. Comorbidity was measured using the Charlson Comorbidity Index (CCI) and age-adjusted Charlson Index (CACI) excluding mCRC as the index disease. Kaplan-Meier survival analysis and Cox regression were used for statistical analysis.

Results: Overall median survival of 266 patients was 14 months. Age ≥ 70 years did not influence survival after local therapies. Similarly, CCI or CACI did not affect the patients prognoses in multivariate analyses. Moderate or severe renal insufficiency ($n = 12$; $p = 0.005$) was the only single comorbidity identified to negatively affect the outcome after local therapy.

Conclusion: Interventional procedures for mCRC may be performed safely even in elderly and comorbid patients. In severe renal insufficiency, the use of invasive techniques should be limited to selected cases.

Keywords: Colorectal cancer, Elderly patients, Comorbidities, Multimodal therapy

Background

Age is a major risk factor for colorectal cancer (CRC) and cancer in general [1]. Elderly patients often suffer from comorbidity and reduced organ function thus requiring particular considerations when making treatment decisions. Additionally elderly patients present a very heterogeneous group with chronological age being insufficient to describe individual resources and deficits. Contributing to these difficulties in decision making, elderly patients are underrepresented in cancer trials while they account for most of the actual patients [2]: When analyzing 495 NCI (National Cancer Institute) studies, Lewis et al. found that only 32% of cancer trial participants were age 65 years and older, in contrast to 61% in the US cancer population [3]. Other authors have published similar results, with an even greater difference for patients aged 70 years and older [4]. Although there is evidence that age should not be a reason to refrain from surgery and chemotherapy, most studies comprise a higher age and comorbidities as exclusion criteria [5–7]. In clinical practice, patients at higher age or with comorbidities often receive the recommended chemotherapies at reduced doses outside

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the standard prescription [8–10]. Yet, the effectiveness of such adapted therapy regimen is unknown.

Local ablative treatments (LAT, e.g. radiofrequency/microwave ablation and interstitial HDR-brachytherapy) as well as locoregional therapies (e.g. Y90 radioembolization) offer local tumor control and extensive cytoreduction with low morbidity and mortality. In oligometastatic disease with few tumor sites and limited number of metastases, LAT can achieve long-term disease control by complete tumor ablation in patients not eligible for surgery [11]. In contrast, locoregional therapies such as Y90 radioembolization may contribute to the overall survival of selected patient by improving the local response in liver-dominant disease or by providing a salvage treatment in chemo-refractory liver metastases [12, 13]. Accordingly, the toolbox of local ablative treatments and locoregional therapies was included in the latest ESMO guideline for colorectal cancer with oligometastatic disease or liver dominant, chemo-refractory metastases [14]. In the context of elderly and comorbid patients, data on the efficacy of LAT is still rare.

This study aims to assess the influence or absence of negative effects of higher age or comorbiditieson the outcome after local therapies. We hypothesize that minimal-invasive local or locoregional techniques add further value by offering broader treatment options in elderly and comorbid patients with metastatic colorectal disease.

Methods

Patient cohort

We searched our institutional data base for all patients with mCRC receiving at least one radiofrequency ablation (RFA), high-dose-rate brachytherapy (HDR-BT) or Y90-radioembolization (Y90-RE) between 2006 and 2010. We included all patients with complete records on patient history and at least one follow up visit.

The study comprised a total of 266 patients (179 male, 87 female; mean age 66 years). One hundred ninety-six patients (73.7%) had synchronous metastases within 12 months after diagnosis of the primary tumor. Nearly all patients presented with hepatic metastases ($n = 251$, 94.4%). Further sites of dissemination included lung ($n = 77$, 28.4%), lymphatic ($n = 44$, 16.5%), osseous ($n = 10$, 3.8%) or other metastases ($n = 22$, 8.3%). Most of the patients failed at least one ($n = 79$, 29.7%) or two ($n = 160$, 60.2%) lines of chemotherapy compromising either irinotecan or oxaliplatin combined with 5-fluorouracil. Additionally, 169 patients (63.5%) received EGFR or VEGF inhibiting therapy. Prior surgical treatments included surgery for the primary tumor in 263 patients (98.9%), resection of hepatic metastases in 91 patients (34.2%) and resection of lung/other metastases in 34 patients (12.8%).

Throughout the observation period, nearly half of the patients developed further liver metastases ($n = 118$, 44.4%) followed by lung metastases ($n = 108$, 40.6%), lymphatic metastases ($n = 51$, 19.2%), osseous metastases ($n = 18$, 6.8%) and other ($n = 73$, 27.4%).

Patients were considered for local ablative treatment and Y90 radioembolization by a multidisciplinary team (MDT; including medical, surgical and radiation oncologists) depending on their stage of disease (e.g. size of tumor, number of lesions, tumor sites) as well as organ function and performance status. Local ablation was selected in potentially resectable metastases only if patients had an unfavorable performance status and/or severe comorbidities (resulting in a high risk of perioperative morbidity and mortality) or if patients refused surgery. Patients with single lesions up to 3 cm in diameter were preferably treated by radiofrequency ablation. If the localization and number of metastases or tumor size above 3 cm limited RFA, interstitial HDR brachytherapy was applied for oligometastatic disease. Patients with diffuse, liver-dominant involvement underwent Y90 radioembolization. In case of tumor progress during follow-up, patients were reassessed by the MDT for the next treatment step, i.e. further local treatment strategies and/or systemic therapy. In total, 732 interventions were performed.

Local and locoregional therapies

The following image guided techniques were considered by the MDT (if not eligible for systemic therapy only).

Radiofrequency ablation

Radiofrequency ablation induces a coagulation necrosis of tumor tissue by generating heat [15]. RFA is considered to be a safe and effective method with major complications occurring in 1–5% of patients. Beside limitations according to proximity to vulnerable organs, RFA underlies a heat-sink effect restricting the maximum size of the coagulation necrosis [16].

In our study, local ablation for smaller lung or liver metastases (< 3 cm) was performed using CT-guided radiofrequency ablation (LeVeen®, Boston Scientific, Natrick, United States or Starburst Semi-Flex®, AngioDynamics, Mountain View, Canada) according to manufacturer's specifications. A total of 21 liver and 77 lung RFA interventions were conducted.

CT guided high-dose rate brachytherapy

CT-guided HDR-BT is an ablative technique utilizing radiation from an Iridium-192 source in afterloading technique. Interstitial catheters were inserted by CT-guidance and subsequent 3D treatment planning was applied (Oncentra®, Nucletron, Veenendaal, The Netherlands). As the catheters are fixed within the tumor, the delivery of

irradiation is not affected by breathing motion. As a consequence, dose delivery to the tumor is highly accurate and exposure of healthy tissues or risk organs can be reduced to a minimum [17].

Since HDR-BT has no systematic restrictions for tumor size and location close to vessels, it was preferably indicated if multiple tumors were present as well as in larger (> 3 cm) liver or lung metastases or any lymphatic metastases [18–20]. To ensure a complete ablation, a target dose of 20Gy in a single session was subscribed [21]. HDR-BT was mainly used for liver ablations ($n = 422$), as well as for ablation of lung metastases ($n = 52$), lymphatic nodes ($n = 9$) and other tumor sites ($n = 8$).

Y90-radioembolization

If number, size or location of liver metastases exceeded the capabilities of local ablation by RFA or HDR-BT, patients were subsequently evaluated for loco-regional radioembolization using microspheres labeled with the beta-emitter Yttrium-90 (half-life 64 h; mean energy 0.96 MeV) administered through an angiographic catheter to the liver arteries [22, 23]. Multinodular liver metastases were treated in 96 cases by 142 radioembolizations using Y90 resin microspheres (SIR-Spheres®, Sirtex Medical, Lane Cove, Australia), the required dose was calculated previously according to the body-surface area method after an initial evaluation with Technecium-99 m macro-aggregated albumin (LyoMAA, Covidien, Neustadt, Germany).

Comorbidity measurement

To assess comorbidities, we used the Charlson Comorbidity Index (CCI) which is validated in older patients with the option to calculate an age adjusted index (Charlson Age Comorbidity Index, CACI) [24, 25] to predict mortality in a range of comorbid conditions. 19 comorbidity items were included and each condition was assigned a score of 1, 2, 3 or 6 (see Table 3), depending on the risk of death associated with each one. The sum of these items (between 0 and 30) formed the final comorbidity index (CCI, CACI) that has been established as a predictor of patient outcome and mortality in different settings and larger populations including cancer patients [26]. The index disease, metastatic colorectal cancer, was excluded when calculating the index. Additional information was assessed regarding typical cardiovascular risk factors not included within the CCI (e.g. hypertension, hyperlipidemia, obesity).

All information on comorbidity was recorded at baseline.

Statistical analysis

SPSS 21.0 (IBM®, New York, USA) was used for the complete analysis set. Comorbidity items including the summary within the CCI/CACI, patient age and key characteristics of disease and treatment underwent a stepwise Cox regression analysis. All baseline variables were initially analyzed in a univariate Cox regression. Any variable scoring a p-value < 0.1 was then included in a multivariate Cox proportional hazard model. Tables 3 and 4 give a summary of the main analysis with p-values, harzard ratios (HR) and 95% confidence intervals (95% CI). Statistical significance in the multivariate analysis was assumed for p-values < 0.05. Visualization was achieved by Kaplan-Meier charts.

Results

Treatment outcome

A total of 732 procedures were performed in all patients, an overview is given in Table 1. All survival data were

Table 1 Overview on procedures and outcome

			Median overall survival (months)[a]			
	Patients	Procedures	Patient age		Comorbidity	
	n	*n*	≥ 70 years	< 70 years	CCI ≥ 3	CCI < 3
RFA	60	99	26.7 m	24.3 m	24.0 m	26.2 m
liver	18	21		**($p = 0.76$)**		**($p = 0.16$)**
lung	42	77				
other	1	1				
HDR-BT	192	491	19.1 m	18.2 m	16.4 m	18.9 m
liver	176	422		**($p = 0.83$)**		**($p = 0.43$)**
lung	29	52				
lymph node	9	9				
other	8	8				
Y90-RE	96	142	6.9 m	6.5 m	5.3 m	6.9 m
				($p = 0.86$)		**($p = 0.21$)**

[a]statistics for overall survival according to Cox regression analysis; p-values (bold) refer to the comparison of survival between age/comorbidity groups

measured beginning with the first treatment at our institution.

RFA patients

Patients initially presenting with singular, small metastases (< 3 cm) confined to lung ($n = 42$) or liver ($n = 18$) were treated by radiofrequency ablation yielding a median survival of 26.7 months and 24.4 months (including further local ablative treatments and/or systemic therapies in case of disease progression). A single RFA treatment was used for the ablation of a vertebral metastasis. 50 out of 60 patients (83%) treated by RFA underwent multiple RFA sessions and/or further treatment by HDR-BT for recurrent metastases.

CT-guided HDR brachytherapy patients

Oligonodular and larger metastases were treated by HDR-BT. Patients with liver metastases eligible for HDR-BT at their first presentation in our department achieved a median survival of 18.1 months ($n = 176$). Initially applying HDR-BT to lung metastases, a median survival of 29.6 months was observed ($n = 29$). Lymphatic nodes and other infrequent localizations of metastases (e.g. adrenal glands, pancreas) were treated exclusively by HDR-BT with a corresponding median survival of 17.0 to 26.7 months. In patients with multiple tumor sites or disease progression during follow up, HDR-BT was repeated ($n = 143$) or Y90-RE performed ($n = 28$).

Radioembolization patients

Ninety- six patients with diffuse liver metastases underwent Y90-RE with a median survival of 6.7 months. 68 of these patients who had failed first and second line chemotherapy including variable treatment cycles with oxaliplatin, irinotecan and 5-fluorouracil demonstrated a significantly shorter median survival of 5.8 months in univariate and multivariate Cox regression analyses ($p < 0.001$). However, 19 salvage patients (28%) undergoing Y90 radioembolization had a survival of at least 9 months with long-term survivors reaching a survival of nearly 30 months. All salvage patients treated by Y90-RE in this cohort represent a majority of patients in a dedicated prognostic analysis which can be reviewed for supplementary information [27].

Impact of palliative chemotherapy after first interventional treatment

A total of 120 patients (45%) received further chemotherapy after the first local treatment. These patients demonstrated an improved survival of 22.0 vs. 16.1 months compared to patients without further systemic therapies ($p = 0.009$; HR 0.71; 95% CI 0.55–0.92).

Table 2 Patient characteristics

	n	%
All patients	266	100.00
Male	179	67.30
Female	87	32.70
First diagnosis		
Mean age (SD) in years	63.0 (+/− 9.7)	
Primary tumor		
located in Colon (C18)	151	56.77
Rectosigmoid junction (C19)	18	6.77
Rectum (C20)	98	36.84
T1,T2	29	10.90
T3,T4	227	85.30
T missing	10	3.80
N0	74	27.80
N1,2	179	67.30
N status missing	13	4.90
Synchronous metastases	166	62.41
Prior treatment		
Systemic chemotherapy	248	93.23
Median lines of chemotherapy (range)	2 (0–8)	
Radiochemotherapy	30	11.28
Surgery for colorectal primary	263	98.87
Radiation therapy for colorectal primary	21	7.89
Surgery for liver metastases	91	34.21
Other local treatment for liver metastases	40	15.04
Surgery for lung metastases	14	5.26
Surgery for other metastases	20	7.52
Local therapy for other metastases	5	1.88
First interventional treatment		
Mean age (SD) in years	66,5 (+/−9.6)	
Age > 70 years	89	33.5
Median Karnofsky index (range) in %	80 (50–100)	
Liver metastases	251	96.99
Liver metastases only	121	45.50
Liver involvement > 25%	45	16.92
Lung involvement	100	37.60
Other	83	31.20
≥ 2 organ systems involved	140	52.63

Outcome by patient characteristics

Overall patient characteristics are outlined in Table 2. Survival in all patients accounted for 14 months, survival analysis was conducted using a stepwise Cox regression analysis. Nearly all patients suffered from liver metastases ($n = 251$). Patients with an initial positive N stage (n

= 179) and metachronous lymph node metastases (n = 44) had a poorer prognosis (13.1 vs 17.0 months; 9.8 vs 16.1 months) after first interventional treatment in univariate analysis, yet multivariate regression analysis did not demonstrate a significant influence on overall survival (p = 0.25 and p = 0.17; respectively).

Synchronous metastases at first diagnosis (n = 166) only had significant influence in univariate analysis (p = 0.036) but not in multivariate analysis (p = 0.90). Metachronous pulmonary metastases had no impact on survival (p = 0.55).

Systemic therapy options after initiation of interventional therapy were stratified by previous failure of either oxaliplatin or irinotecan based combined regimen (second line, n = 79) or failure of both (third line, n = 160). Patients without prior chemotherapy were classified to first line (n = 27), including patients with contraindications to systemic therapy. A median survival of 13.2 vs. 16.6 months was observed in patients receiving third line therapy compared to patients in earlier lines of therapy without prognostic influence in multivariate analysis (p = 0.30).

If third line patients were still eligible for local-ablative techniques (RFA and/or HDR-BT), the median survival reached 17.5 months (n = 114).

The complete multivariate analysis is demonstrated in Table 4.

Age analysis

Our cohort included 89 patients (33.5%) 70 years or older. This patient group demonstrated no altered survival as compared to younger patients after first interventional therapy in a Cox regression analysis (p = 0.19; HR 0.84; 95% CI 0.64–1.10). Median survival in the subgroup of elder patients was 16.6 vs. 13.2 months as shown in Fig. 1.

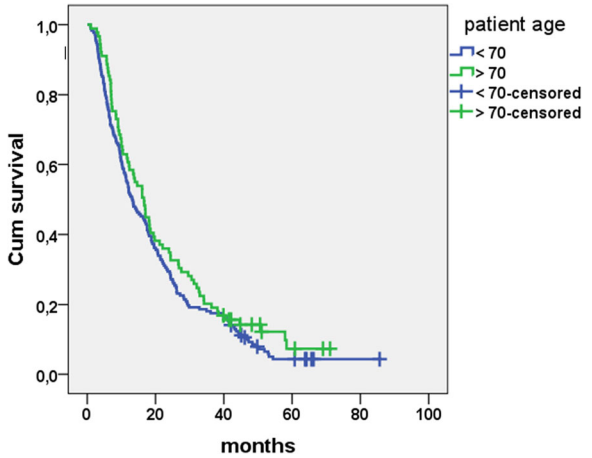

Fig. 1 Overall survival by age. Kaplan Meier estimation for overall survival after first treatment by age < 70 (13.2 months; n = 177) and age ≥ 70 (16.6 months; n = 89), no statistical difference between groups (p = 0.19; Cox regression analysis)

In patients older than 70 years initial or additional lymphatic metastases were of no prognostic value (p = 0.11; HR 1.24; 95% CI 0.95–1.61 and p = 0.23; HR 1.62; 95% CI 0.74–3.54), just as for heavily pretreated patients with at least three lines of systemic chemotherapy (p = 0.18; HR 1.23; 95% CI 0.91–1.67). Survival of elderly versus younger patients was similar regarding the first technique applied (RFA, HDR-BT or Y90-RE) in regression analysis, see Table 1.

Comorbidity analysis (CCI, CACI)

With a sum of 3 points or more for the CCI, 43 patients (16.2%) displayed severe comorbidities at baseline. These comorbidities were significantly more frequent in older patients ≥70 years (n = 21; 23.6%) than in younger patients < 70 years (n = 22; 12.4%; p = 0.023; Chi-Square test). According to the age adjusted CACI, a total of 112 patients (42.1%) were considered with severe comorbidities at first therapy. An overview of CCI/CACI in the patient cohort is given in Table 3.

In a univariate Cox regression, both CCI or CACI ranging from 0 to 7 and 0–8 had no significant impact on the patients prognosis (p = 0.82; p = 0.86), respectively. Comparison of patients with severe comorbidities (CCI ≥ 3) versus no or moderate comorbidities demonstrated no significant influence on overall survival either (18.8 months vs. 21.9 months; p = 0.41; see Fig. 2). Regression analysis of all single items summarized in the index (see Table 3) revealed a significant influence of moderate or severe renal disease in 12 patients (p = 0.005). Two patients with gastric or duodenal ulcer died after 3.7 and 5.7 months, respectively (p = 0.006). Patients with chronic pulmonary disease (n = 29) had a lower hazard ratio (p = 0.006; HR 0.61; 95 CI 0.38–0.99). No other comorbidity item had a considerable impact, despite 55 patients suffering from peripheral vascular disease and 36 patients with a history of myocardial infarction or coronary heart disease (p = 0.81 and p = 0.38). Multivariate regression analysis finally confirmed a statistical significant impact of moderate or severe renal disease in all patients (p = 0.005).

Apart from the conditions reflected in the CCI, 116 patients had been diagnosed with hypertension (43.6%), 18 patients with obesity (6.8%) and 20 with hyperlipidemia (7.5%). None of these factors demonstrated a significant influence on survival as demonstrated in Table 4.

Discussion

Interventional oncology in elderly patients

Metastatic colorectal cancer continues to be a major therapeutic challenge especially in elderly patients as prevalence of comorbidity is considered to be more frequent compared to the background population [28]. The corresponding interaction between cancer and comorbidity, and whether comorbidity leads to cancer

Table 3 Prevalence of comorbidities according to the Charlson Comorbidity index

CCI[a]	condition	*n*	%	*p*-value°	HR (95% CI)
1	myocardial infarction, coronary artery disease	36	13,5	0.38	0.85 (0.58–1.23)
	congestive heart failure	15	5,6	0.62	0.87 (0.51–1.50)
	peripheral vascular disease	55	20,7	0.81	0.96 (0.71–1.31)
	cerebrovascular disease	13	4,9	0.58	0.85 (0.48–1.52)
	dementia	0	0		
	chronic pulmonary disease	21	7,9	0.046	0.61 (0.38–0.99)
	connective tissue disorder	2	0,8	0.93	0.94 (0.23–3.78)
	peptic ulcer disease	2	0,8	0.006	7.40 (1.80–30.50)
	mild liver disease	10	3,8	0.26	1.44 (0.76–2.72)
	diabetes without complications	42	15,8	0.94	0.99 (0.70–1.40)
2	diabetes with end-organ damage	17	6,4	0.74	0.92 (0.55–1.52)
	hemiplegia	1	0,4	0.70	1.48 (0.21–10.61)
	moderate/severe renal disease	12	4,5	0.005	2.3 (1.29–4.13)
	any tumor without metastases (incl. Leukemia, lymphoma)	34	12,8	0.89	1.03 (0.71–1.50)
3	moderate/severe liver disease	3	1,1	0.33	1.77 (0.57–5.55)
6	metastatic solid tumor (mCRC excluded)	0	0		
	AIDS	0	0		
8	AIDS and any tumor	0	0		

[a]age adjusted index CACI adds 1 point for each decade after 40 years
°statistics for overall survival according to univariate Cox regression, variables with univariate p < 0.1 are processed in Table 4

diagnosis in earlier or later stages, is still object to ongoing discussions [29]. Furthermore, elderly and multimorbid patients are often not eligible for surgery or efficacious polychemotherapies [30].

In our group of metastatic CRC patients, about 62% had comorbidities according to the CCI. Adding conditions as hypertension, hyperlipidemia and obesity, 71% of patients were suffering from comorbidities, which is far more frequent than in other studies applying the CCI reporting a prevalence between 32 and 41% in metastatic or non-metastatic CRC patients [31].

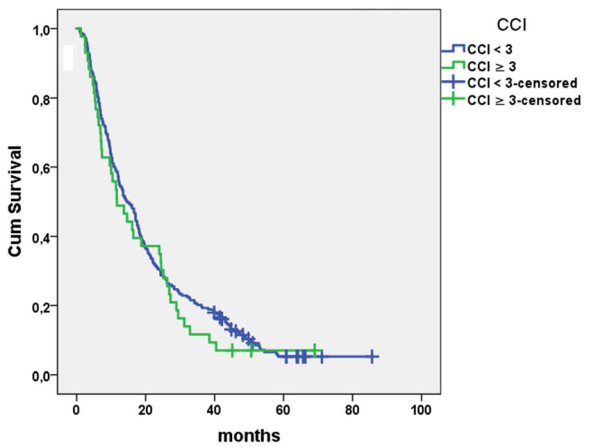

Fig. 2 Overall survival by CCI. Kaplan Meier estimation for overall survival after first treatment separated by Charlson Comorbidity Index < 3 (21.9 months; *n* = 223) and ≥ 3 (18.1 months; *n* = 43); no statistical difference between groups (*p* = 0.41; Cox regression analysis)

Median survival after RFA as first local treatment of liver metastases was 24.4 months in our patients, which is consistent with existing data ranging from 24 to 36 months [32].

As HDR-BT is usually applied in metastases exceeding the technical feasibility of RFA in size and number, thus adding an unfavorable prognosis bias, a corresponding median survival of 18.1 months was found in those patients. A retrospective analysis by Collettini et al. demonstrated a comparable median survival of 18 months after HDR-BT of colorectal liver metastases [33].

Most patients undergoing Y90-radioembolization had previously failed all accessible chemotherapies leading to a median survival of 5.8 months in this group. However, one quarter of these patients survived 9 or more months including a small group of long term survivors > 2 years indicating that patient selection is of utmost importance in a salvage population [34]. This could be shown by our group in a previous study regarding the prognostic value of Karnofsky index, tumor load and tumor markers in patients undergoing Y90-radioembolization to help selecting appropriate patients [27].

When applying CCI and CACI to measure the prognostic impact of comorbidities in our patients, we did not observe a relation of higher index values with overall

Table 4 Stepwise Cox regression analysis of key characteristics at baseline including CCI items with univariate $p < 0.1$ (all items of CCI are shown in Table 3)

Variable	Univariate *p*	HR (95% CI)	Multivariate *p**	HR (95% CI)
CCI items p < 0.1				
Chronic pulmonary disease	0.046*	0.61 (0.38–0.99)	0.30	0.76 (0.45–1.28)
Peptic ulcer disease	0.006*	7.40 (1.80–30.50)	0.17	2.75 (0.65–11.69)
Moderate/severe renal disease	0.005*	2.3 (1.29–4.13)	0.005	2.46 (1.32–4.57)
Comorbidities not included in CCI				
Hypertension	0.54	0.93 (0.72–1.20)		
Obesity	0.32	0.77 (0.47–1.28)		
Hyperlipidemia	0.48	0.84 (0.51–1.37)		
Patient and treatment characteristics				
Age > 70 years	0.19	0.84 (0.64–1.10)		
CCI ≥ 3	0.41	1.15 (0.82–1.62)		
Positive N stage of primary	0.004*	1.27 (1.08–1.50)	0.25	1.11 (0.93–1.33)
Synchronous metastases	0.036*	1.36 (1.02–1.81)	0.90	0.98 (0.71–1.35)
Metachronous lymph node metastases	0.032*	1.44 (1.03–2.00)	0.17	1.31 (0.89–1.91)
Metachronous pulmonary metastases	0.55	1.09 (0.83–1.43)		
1st/2nd Line vs. 3rd Line treatment	0.001*	0.83 (0.77–0.90)	0.30	0.89 (0.72–1.1)
Salvage treatment in Y90-RE	0.001*	2.17 (1.37–3.45)	< 0.001	4.35 (3.06–6.17)

*multivariate Cox regression analysis including all variables $p < 0.1$ in univariate analysis

survival. It should be noted that about 42% of all patients had severe comobidities according to the age-adjusted index (CACI≥3). This finding supports the assumption that local ablative therapies such as RFA or HDR-BT, or a locoregional treatment such as Y90 radioembolization, can be safely applied in risk patients with a moderate toxicity profile or adverse event rate, respectively.

A similar relationship was seen recently by Jehn et al. in patients undergoing systemic therapy for mCRC as CCI and age showed no influence on survival [35]. In this population, adverse events were not found to be more frequent in elderly patients, although a significantly higher CCI was observed. Also response rates and survival were balanced irrespective of age and comorbidity. Further studies even discuss inferior outcome in younger patients, most probably caused by more aggressive tumor biology as compared to elder patients [36, 37]. With regard to our patients treated by local therapies, we observed a similar trend potentially related to a more favorable tumor biology in the eldery.

Implications

Our study has demonstrated that older age or a higher rate of comorbidities with age (CCI and CACI) do not influence survival in metastatic colorectal cancer when patients are selected for local or loco-regional ablation by RFA, HDR-BT or Y90 radioembolization. A poorer survival was only seen in patients with moderate or severe renal impairment in our multivariate analysis. Renal disease in general is associated with a poor prognosis and has been reported to have a specifically negative impact on survival in different cancer populations [38].

Limitations

A possible source of error in our analysis may result from data being derived from discharge diagnoses or follow up documentation in our own medical hospital records. Conditions treated by the general practitioner or subsequently in other hospitals may not have been completely represented in our data as a result of the studies retrospective nature. Furthermore, our sample is not necessarily representative for all mCRC patients with a comparatively high frequency of comorbidities in our cohort as compared to other studies. However, we hypothesize that these finding exclude a positive selection in our cohort.

Conclusion

The tool box of image guided treatments proved to be safe and applicable even in patients of higher age or patients presenting with comorbidities. Our study results support offering ablative treatments to metastatic colorectal cancer patients even at advanced age or high Charlson indices.

Abbreviations

CACI: Charlson Age Comorbidity Index; CCI: Charlson Comorbidity Index; CT: Computed tomography; ESMO: European Society for Medical Oncology; HDR-BT: High-dose rate brachytherapy; mCRC: metastatic colorectal cancer; MRI: magnetic resonance imaging; RFA: Radiofrequency ablation; Y90-RE: Y90-radioembolization

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Availability of data and materials
All relevant data regarding the study conclusion are displayed in the publication. Raw data used and/or analysed during the study are available from the corresponding author on reasonable request.

Authors' contributions
RS and RD participated in the design of the study, carried out data analysis and statistical work, drafted the manuscript. JE helped in the organization of the study and performed data acquisition and interpretation. MS participated in the design of the study and helped to revise the manuscript. KM and PH participated in the data acquisition and data interpretation. MP and HA participated in the design of the study and performed data interpretation. JR participated in the design of the study, helped drafting the manuscript and carried out the final revision. All authors have given final approval for the manuscript and takes public responsibility.

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki. All patients included were treated at a single institution, retrospective data collection and analysis was approved by the local ethics committee (Otto-von-Guericke University Magdeburg). All patients gave written informed consent for the collection of their medical data for scientific purposes.

Consent for publication
No personal information is included in the publication, thus no dedicated approval was required.

Competing interests
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References

1. Balducci L. Geriatric oncology: challenges for the new century. Eur J Cancer. 2000;36(14):1741–54.
2. Aapro MS, Kohne CH, Cohen HJ, Extermann M. Never too old? Age should not be a barrier to enrollment in cancer clinical trials. Oncologist. 2005;10(3):198–204.
3. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, Housman MG, Escarce JJ. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol. 2003;21(7):1383–9.
4. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol. 2004;22(22):4626–31.
5. Basdanis G, Papadopoulos VN, Michalopoulos A, Fahantidis E, Apostolidis S, Berovalis P, Zatagias A, Karamanlis E. Colorectal cancer in patients over 70 years of age: determinants of outcome. Tech Coloproctol. 2004;8(Suppl 1):s112–5.
6. Etzioni DA, El-Khoueiry AB, Beart RWJ. Rates and predictors of chemotherapy use for stage III colon cancer: a systematic review. Cancer. 2008;113(12):3279–89.
7. Keating NL, Landrum MB, Klabunde CN, Fletcher RH, Rogers SO, Doucette WR, Tisnado D, Clauser S, Kahn KL. Adjuvant chemotherapy for stage III colon cancer: do physicians agree about the importance of patient age and comorbidity? J Clin Nutr. 2008;26(15):2532–7.
8. Daniele B, Croitoru A, Papandreou C, Bronowicki JP, Mathurin P, Serejo F, Stal P, Turnes J, Ratziu V, Bodoky G. Impact of sorafenib dosing on outcome from the European patient subset of the GIDEON study. Future Oncol. 2015;11(18):2553–62.
9. Nakayama G, Tanaka C, Uehara K, Mashita N, Hayashi N, Kobayashi D, Kanda M, Yamada S, Fujii T, Sugimoto H, et al. The impact of dose/time modification in irinotecan- and oxaliplatin-based chemotherapies on outcomes in metastatic colorectal cancer. Cancer Chemother Pharmacol. 2014;73(4):847–55.
10. Venderbosch S, Doornebal J, Teerenstra S, Lemmens W, Punt CJ, Koopman M. Outcome of first line systemic treatment in elderly compared to younger patients with metastatic colorectal cancer: a retrospective analysis of the CAIRO and CAIRO2 studies of the Dutch colorectal Cancer group (DCCG). Acta Oncol. 2012;51(7):831–9.
11. de Baere T, Tselikas L, Yevich S, Boige V, Deschamps F, Ducreux M, Goere D, Nguyen F, Malka D. The role of image-guided therapy in the management of colorectal cancer metastatic disease. Eur J Cancer. 2017;75:231–42.
12. Kennedy A, Cohn M, Coldwell DM, Drooz A, Ehrenwald E, Kaiser A, Nutting CW, Rose SC, Wang EA, Savin MA. Updated survival outcomes and analysis of long-term survivors from the MORE study on safety and efficacy of radioembolization in patients with unresectable colorectal cancer liver metastases. J Gastrointest Oncol. 2017;8(4):614–24.
13. Sangha BS, Nimeiri H, Hickey R, Salem R, Lewandowski RJ. Radioembolization as a treatment strategy for metastatic colorectal Cancer to the liver: what can we learn from the SIRFLOX trial? Curr Treat Options in Oncol. 2016;17(6):26.
14. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386–422.
15. Buscarini E, Savoia A, Brambilla G, Menozzi F, Reduzzi L, Strobel D, Hansler J, Buscarini L, Gaiti L, Zambelli A. Radiofrequency thermal ablation of liver tumors. Eur Radiol. 2005;15(5):884–94.
16. Lin ZY, Li GL, Chen J, Chen ZW, Chen YP, Lin SZ. Effect of heat sink on the recurrence of small malignant hepatic tumors after radiofrequency ablation. J Cancer Res Ther. 2016;12(Supplement):C153–8.
17. Peters N, Wieners G, Pech M, Hengst S, Ruhl R, Streitparth F, Lopez Hanninen E, Felix R, Wust P, Ricke J. CT-guided interstitial brachytherapy of primary and secondary lung malignancies: results of a prospective phase II trial. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]. 2008;184(6):296–301.
18. Collettini F, Singh A, Schnapauff D, Powerski MJ, Denecke T, Wust P, Hamm B, Gebauer B. Computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of metastases adjacent to the liver hilum. Eur J Radiol. 2013;82(10):e509–14.
19. Ricke J, Wust P, Wieners G, Beck A, Cho CH, Seidensticker M, Pech M, Werk M, Rosner C, Hanninen EL, et al. Liver malignancies: CT-guided interstitial brachytherapy in patients with unfavorable lesions for thermal ablation. J Vasc Interv Radiol. 2004;15(11):1279–86.
20. Wieners G, Pech M, Rudzinska M, Lehmkuhl L, Wlodarczyk W, Miersch A, Hengst S, Felix R, Wust P, Ricke J. CT-guided interstitial brachytherapy in the local treatment of extrahepatic, extrapulmonary secondary malignancies. Eur Radiol. 2006;16(11):2586–93.
21. Ricke J, Mohnike K, Pech M, Seidensticker M, Ruhl R, Wieners G, Gaffke G, Kropf S, Felix R, Wust P. Local response and impact on survival after local ablation of liver metastases from colorectal carcinoma by computed tomography-guided high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys. 2010;78(2):479–85.
22. Jakobs TF, Hoffmann RT, Dehm K, Trumm C, Stemmler HJ, Tatsch K, La Fougere C, Murthy R, Helmberger TK, Reiser MF. Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. J Vasc Interv Radiol. 2008;19(8):1187–95.
23. Kennedy AS, Coldwell D, Nutting C, Murthy R, Wertman DE Jr, Loehr SP, Overton C, Meranze S, Niedzwiecki J, Sailer S. Resin 90Y-microsphere

brachytherapy for unresectable colorectal liver metastases: modern USA experience. Int J Radiat Oncol Biol Phys. 2006;65(2):412–25.
24. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47(11):1245–51.
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
26. Ouellette JR, Small DG, Termuhlen PM. Evaluation of Charlson-age comorbidity index as predictor of morbidity and mortality in patients with colorectal carcinoma. J Gastrointest Surg. 2004;8(8):1061–7.
27. Damm R, Seidensticker R, Ulrich G, Breier L, Steffen IG, Seidensticker M, Garlipp B, Mohnike K, Pech M, Amthauer H, et al. Y90 Radioembolization in chemo-refractory metastastic, liver dominant colorectal cancer patients: outcome assessment applying a predictive scoring system. BMC Cancer. 2016;16:509.
28. Jorgensen TL, Hallas J, Friis S, Herrstedt J. Comorbidity in elderly cancer patients in relation to overall and cancer-specific mortality. Br J Cancer. 2012;106(7):1353–60.
29. Sogaard M, Thomsen RW, Bossen KS, Sorensen HT, Norgaard M. The impact of comorbidity on cancer survival: a review. Clin Epidemiol. 2013;5(Suppl 1):3–29.
30. Lund CM, Vistisen KK, Dehlendorff C, Ronholt F, Johansen JS, Nielsen DL. The effect of geriatric intervention in frail elderly patients receiving chemotherapy for colorectal cancer: a randomized trial (GERICO). BMC Cancer. 2017;17(1):448.
31. Ostenfeld EB, Norgaard M, Thomsen RW, Iversen LH, Jacobsen JB, Sogaard M. Comorbidity and survival of Danish patients with colon and rectal cancer from 2000-2011: a population-based cohort study. Clin Epidemiol. 2013; 5(Suppl 1):65–74.
32. Solbiati L, Livraghi T, Goldberg SN, Ierace T, Meloni F, Dellanoce M, Cova L, Halpern EF, Gazelle GS. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. Radiology. 2001;221(1):159–66.
33. Collettini F, Lutter A, Schnapauff D, Hildebrandt B, Puhl G, Denecke T, Wust P, Gebauer B. Unresectable colorectal liver metastases: percutaneous ablation using CT-guided high-dose-rate brachytherapy (CT-HDBRT). Rofo. 2014;186(6):606–12.
34. Seidensticker R, Denecke T, Kraus P, Seidensticker M, Mohnike K, Fahlke J, Kettner E, Hildebrandt B, Dudeck O, Pech M, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol. 2012;35(5):1066–73.
35. Jehn CF, Boning L, Kroning H, Pezzutto A, Luftner D. Influence of comorbidity, age and performance status on treatment efficacy and safety of cetuximab plus irinotecan in irinotecan-refractory elderly patients with metastatic colorectal cancer. Eur J Cancer. 2014;50(7):1269-75.
36. Bakogeorgos M, Mountzios G, Kotsantis G, Economopoulou P, Fytrakis N, Kentepozidis N. Chemotherapy compliance, tolerance and efficacy in elderly and non-elderly patients with metastatic colorectal cancer: a single institution comparative study. J BUON. 2013;18(3):629–34.
37. Steele SR, Park GE, Johnson EK, Martin MJ, Stojadinovic A, Maykel JA, Causey MW. The impact of age on colorectal cancer incidence, treatment, and outcomes in an equal-access health care system. Dis Colon Rectum. 2014; 57(3):303–10.
38. Sarfati D, Gurney J, Lim BT, Bagheri N, Simpson A, Koea J, Dennett E. Identifying important comorbidity among cancer populations using administrative data: prevalence and impact on survival. Asia Pac J Clin Oncol. 2013;12(1):e47-56.

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Veröffentlichung 12

Ultrasound-assisted catheter placement in CT-guided HDR brachytherapy for the local ablation of abdominal malignancies: Initial experience.

Damm R, El-Sanosy S, Omari J, Damm R, Hass P, Pech M, Powerski M.

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Thieme

Ultrasound-assisted catheter placement in CT-guided HDR brachytherapy for the local ablation of abdominal malignancies: Initial experience

Ultraschallassistierte Katheteranlage bei der CT-geführten HDR-Brachytherapie zur lokalen Ablation abdomineller Malignome: erste Erfahrungen.

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ABSTRACT

Purpose To evaluate the safety and feasibility of sonographically-assisted catheter placement in interstitial high-dose-rate brachytherapy of abdominal malignancies.

Materials and Methods In an initial cohort of 12 patients and 16 abdominal tumors (colorectal liver metastases n = 9; renal cell cancer n = 3; hepatocellular carcinoma n = 2; cholangiocellular carcinoma n = 2), initial puncture and catheter placement for CT-guided brachytherapy were performed under sonographic assistance when possible. The interventional procedure was prospectively recorded and in-patient data were collected. All data underwent descriptive statistics and comparative analysis by the Mann-Whitney test.

Results In 12 out of 16 lesions (diameter 1.5 – 12.9 cm), initial puncture was successfully achieved under ultrasound guidance without utilization of CT fluoroscopy, yielding a significantly shorter mean total fluoroscopy time (14.5 vs. 105.5 s; p = 0.006). In 8 lesions visibility was rated better in ultrasound than in CT fluoroscopy (p = 0.2). No major or minor complications occurred within 30 days after treatment.

Conclusion Ultrasound-assisted catheter placement during interstitial CT-guided brachytherapy of abdominal tumors could improve catheter positioning and reduce radiation exposure for medical staff.

Key points Ultrasound-assisted catheter placement in CT-guided brachytherapy is safe and feasible. Ultrasound puncture may improve catheter positioning. Reduced CT fluoroscopy time can significantly help to minimize radiation exposure for medical staff.

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ZUSAMMENFASSUNG

Ziel Evaluierung der Sicherheit und Machbarkeit der sonografisch assistierten Katheter-Anlage bei der interstitiellen High-dose-rate-Brachytherapie abdomineller Malignome.

Material und Methoden In einer ersten Kohorte von 12 Patienten mit 16 abdominellen Tumoren (kolorektale Lebermetastasen n = 9; Nierenzellkarzinom n = 3; hepatozelluläres Karzinom n = 2; cholangiozelluläres Karzinom n = 2) erfolgte die initiale Punktion und Katheter-Anlage bei der CT-gestützten Brachytherapie soweit möglich unter sonografischer Führung. Die Durchführung des Eingriffs wurde prospektiv erfasst und der klinische Verlauf der Patienten dokumentiert. Die erhobenen Daten wurden deskriptiv ausgewertet und mit dem Mann-Whitney-U-Test analysiert.

Ergebnisse Bei 12 von 16 Läsionen (Diameter 1,5 – 12,9 cm) konnte die initiale Punktion zur Katheter-Platzierung sonogra-

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fisch erfolgreich ohne Zuhilfenahme der CT-Fluoroskopie vorgenommen werden, wodurch sich die mittlere Fluoroskopiezeit des gesamten Eingriffs signifikant verkürzen ließ (14,5 vs. 105,5 s; p = 0,006). Bei 8 Läsionen wurde die Sichtbarkeit im Ultraschall insgesamt besser bewertet als in der CT-Fluoroskopie (p = 0,2). Es traten keine Minor- oder Majorkomplikationen innerhalb von 30 Tagen auf.

Schlussfolgerung Die ultraschallassistierte Katheter-Anlage könnte bei der interstitiellen, CT-gestützten Brachytherapie abdomineller Tumore sowohl zur verbesserten Katheter-Positionierung als auch zur Reduzierung der Strahlenexposition des medizinischen Personals beitragen.

Introduction

CT-guided interstitial brachytherapy (HDR-BT) is a catheter-based procedure that, among other things, allows local ablation of thoracic and abdominal malignancies.

The irradiation catheter is usually positioned percutaneously using CT fluoroscopy.

Unlike thermal ablation procedures, such as radiofrequency ablation (RFA) and microwave ablation (MWA), this treatment method has no technical limitation regarding tumor size and proximity to heat-vulnerable structures [1, 2]. Furthermore, interstitial irradiation is not subject to any thermal cooling effects by adjacent vessels and has no influence on respiratory excursion due to the fixed placement of the irradiation catheter in the tumor in relation to stereotaxis (SBRT) [3, 4].

Multiple catheters need to be introduced for multiple and larger lesions resulting in a complex procedure typically associated with higher radiation exposure for the radiologist [5, 6]. Furthermore, the accessibility, especially of smaller lesions, under CT fluoroscopy is often difficult and requires experience to reach the target lesion in a dose-saving manner [7, 8].

In thermal ablation procedures, such as radiofrequency ablation, in addition to computer tomography, ultrasound in image guidance has become established and thus represents an alternative to ionizing radiation [9].

In this study we report initial experiences with sonographically-assisted catheter positioning in the interstitial brachytherapy of hepatic and renal malignancies as a supplement to CT fluoroscopy.

Materials and Methods

Patient Cohort

Since July 2017 patients have been recruited and included in a prospective feasibility study. The inclusion criteria include patients with planned, interstitial brachytherapy for the ablation of tumors in sonographically clearly visible organs such as the liver and kidneys. The study was reviewed and approved by the local ethics committee. Prior to the procedure all patients provided their informed consent to study-specific activities and approved the further processing of their clinical and radiographic data for study purposes in accordance with data protection guidelines.

Twelve patients were included (8 men, 4 women, mean age 70 years) with a total of 16 tumors to be treated (colorectal liver metastases n = 9, renal cell carcinomas n = 3, hepatocellular carcinomas n = 2 and cholangiocarcinomas n = 2).

Three patients had prior liver surgery, one patient with a trisectectomy and two patients with atypical resection. Of the 13 liver lesions treated, five were local recurrences after radiofrequency ablation or atypical resection.

To objectify patient selection, a pre-interventional evaluation of sonographic accessibility was dispensed with.

Sonographically-assisted CT-supported Brachytherapy

The catheter placement was performed in an 80-row CT unit (Aquillion Prime, Canon Medical Systems, Neuss, Germany) with concomitant analgosedation of the patient with on-demand, intravenous administration of fentanyl and midazolam under pulse oximetry monitoring. The interstitial access to the target lesion was performed via an initial, image-guided puncture (if possible, sonographically-guided, otherwise performed CT-fluoroscopically) with an 18Ga coaxial needle and the subsequent change to 25cm-long 6F catheter sheaths (Terumo Radifocus® Introducer II, Terumo Europe, Leuven, Belgium) over a stiff guidewire (Amplatz SuperStiff ™, Boston Scientific, Marlborough, USA). A 6F irradiation catheter (afterloading catheter, Primed® Medizintechnik GmbH, Halberstadt, Germany) was placed flush with the inner lumen of the sheath and the system was fixed with a skin suture.

If the lesions were small and round (< 4 cm), an irradiation catheter was inserted into a central position. In the case of a larger or irregularly shaped lesion, multiple catheters were inserted to match the shape of the ablation zone (depending on the access path in a fanned or crossed arrangement).

Once the patient was brought into the radiotherapy site, treatment planning was carried out using a planning CT (Oncentra® Brachy, Elekta Instrument AB, Stockholm, Sweden) and single fraction irradiation with an iridium 192 source used in afterloading technique. After defining the gross tumor volume (GTV) based on the available image information, a safety margin of 5 mm was added for the computer-assisted generation of the clinical target volume (CTV). Due to the stable catheter position in the target volume, the CTV could then be equated with the final planning target volume (PTV). Depending on the tumor entity, a target dose of 15 Gy (renal cell carcinoma, hepatocellular carcinoma), 20 Gy (cholangiocarcinoma carcinoma) or 25 Gy (colorectal liver metastasis) was prescribed for CTV/PTV.

Within the study, CT fluoroscopy (120 kVp / 30 mAs, 0.5 s rotation time, 6 mm single-slice acquisition, image matrix 512 × 512) was replaced by laterally-positioned sonography using low-frequency convex (1 – 5 MHz) and matrix (1 – 6 MHz) ultrasound heads (EPIQ7, Philips Medical Systems, Amsterdam, The Netherlands) during the initial puncture and interim position monitoring

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as often as technically feasable (see ▶ **Fig. 1**). The free-hand puncture technique was used for eight lesions, while four lesions were punctured via a coaxial guide on the ultrasound head.

At the end of each procedure, contrast-enhanced computed tomography was performed as needed to perform radiotherapy planning.

Two specialists in radiology with 7 and 4 years experience in percutaneous interventions (at least 1000 and 300 documented percutaneous interventions, respectively) were responsible for the performance and assessment of the interventions.

Study Design and Statistics

Patient characteristics, the number of catheters per imaging modality, intervention and lesion, lesion parameters, and fluoroscopy times were tabulated. The image datasets were recorded for each intervention performed, and the visibility of the lesions by the intervention radiologists involved was assessed by consensus using a grading scale. In addition, the dose information (CTV, target dose, D100) of all lesions treated was collected from the treatment planning system.

The Society for Interventional Radiology (SIR) classification was used to evaluate major and minor complications [10].

The collected data were first descriptively evaluated in SPSS 24.0 (IBM® SPSS® Statistics, IBM Deutschland GmbH, Ehningen, Germany) with determination of mean and standard deviation as well as median and spread. Box plots were used to illustrate the data. If a comparison of statistical variables between CT and ultrasound imaging modalities was methodically feasible in the small patient population, this was done by the Mann-Whitney U test for independent samples and the Wilcoxon signed-rank test.

Results

Image-guided Catheter Positioning

A total of 16 tumors with a mean diameter of 3.9 ± 2.7 cm (min 1.5 cm to max. 12.9 cm) were treated using 2.3 ± 1.5 irradiation catheters (1 to 5 catheters per lesion, 28 catheters in total).

Catheter positioning could be completely achieved under ultrasound guidance in 12 of 16 lesions and 23 of 28 catheters. In 4 tumors, the initial puncture had to be performed under CT fluoroscopy due to insufficient sonographic conditions. One liver lesion was directly beneath the diaphragm at a resection margin after trisectorectomy and another directly in the liver hilus. In 2 other tumors, sonographic visibility was not considered sufficient for an accurate puncture.

On the whole, all punctures and catheter placements of kidney tumors and liver tumors in the caudal segment row (segment 3/4B/5/6) were successfully performed sonographically. In one patient with a lesion not visible in CT, sonographically-assisted puncture and catheter placement completely replaced CT fluoroscopy (see ▶ **Fig. 2**). Here, only computed tomography with contrast agent application was necessary for radiation planning.

The planned target volume (CTV) dose was achieved in 14 of 16 lesions. In two cases the dose was reduced due to the proximity of the tumor treated to risk organs (gall bladder, maximum dose of 20 Gy, stomach / duodenum, maximum dose of 14 Gy).

▶ **Fig. 1** Arrangement in the CT room for ultrasound-assisted punctures.

Fluoroscopy Time and Lesion Visibility

In some cases of ultrasound-guided intervention, interim catheter placement controls were performed using CT fluoroscopy (120 kVp / 30 mAs, 0.5 s rotation time, 6 mm single-slice acquisition, image matrix 512 × 512). Mean fluoroscopy time for otherwise sonographically-guided procedures, however, was significantly shorter ($p = 0.006$, see ▶ **Fig. 3**) at 14.5 s versus 105.5 s when CT fluoroscopy was used for the whole procedure.

The visibility of the target lesions was assessed based on the consensus of the two radiologists for both imaging modalities. In sonography, recognizability was rated as very good in 8 out of 16 lesions based on graded assessments; in CT fluoroscopy, this was only true for 2 lesions. Four or seven lesions were graded as good, two or five were considered satisfactory. In 2 tumors there was deficient detectability in the ultrasound (two cholangiocarcinomas) or CT (one hepatocellular carcinoma, one colorectal liver metastasis). Other grades were not issued in the low number of cases. ▶ **Fig. 4** provides an overview of the assessment of lesion visibility. Statistically, there was no significant difference between the modalities ($p = 0.27$), although visibility was better in sonography compared to CT in a total of 6 lesions.

Interstitial Tumor Ablation

The tumor-enclosing dose during single fraction irradiation was set at 15 to 25 Gy, depending on the tumor entity, and the mean

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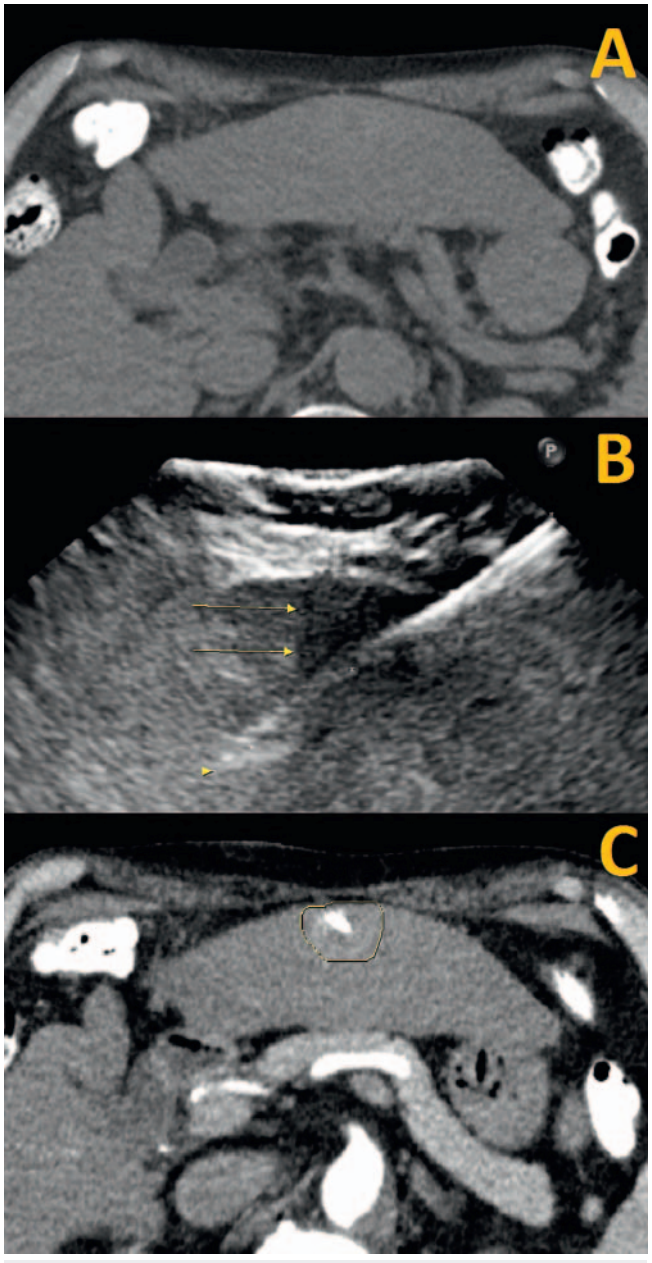
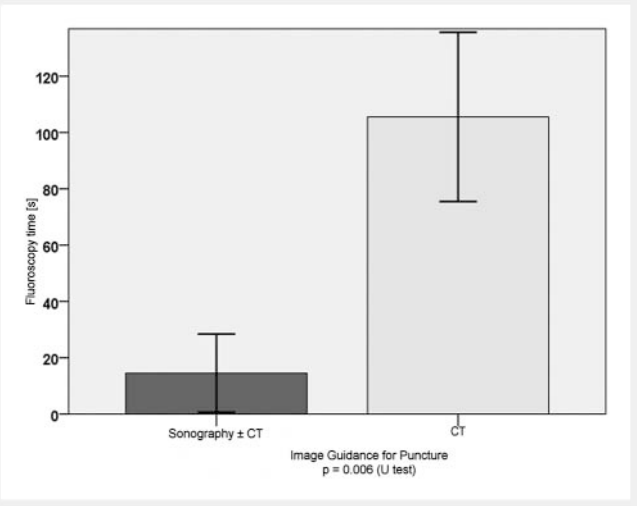
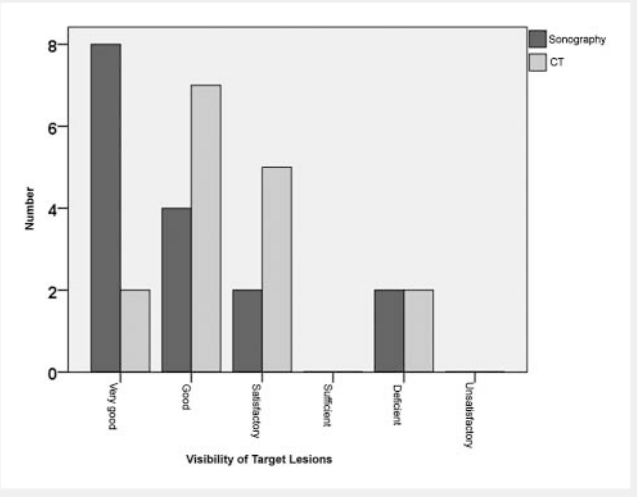


▶ **Fig. 2** Interstitial brachytherapy of a subcapsular HCC in liver segment III. The lesion is barely visible in non-enhanced CT **A** although being detected in previous MRI. Sonography **B** demonstrates a good visualization of the HCC as a hypoechogenic mass (arrows) and is easily punctured (arrow head depicting the needle tip). Contrast-enhanced CT in the arterial phase for irradiation planning **C** showing a central location of the catheter in the HCC (circle).

target dose was 20.6 ± 4.0 Gy. With respect to the clinical target volume (CTV), the final dose distribution (D100) reached the target dose in 14 out of 16 cases, averaging 19.3 ± 4.8 Gy. In two patients, the reason for the reduced dose was the proximity of the tumor to neighboring radiation-sensitive organs (stomach n = 1, duodenum n = 1).



▶ **Fig. 3** Mean fluoroscopy time (± standard deviation) for ultrasound-assisted puncture (Sonography ± CT) vs. CT puncture alone (CT) during catheter placement.



▶ **Fig. 4** Visibility of the target lesion (n = 16) by imaging modality (sonography vs. CT).

Complications

After removal of the catheter sheaths, a sonographic or CT check was carried out after approximately two hours to rule out acute hemorrhaging in all cases.

At the 30-day follow-up, no major or minor complications were observed in the patient population after sonographically-assisted or direct CT fluoroscopic catheter placement.

Discussion

To the best of our knowledge, this feasibility study was the first to utilize sonography during image-guided interstitial HDR brachytherapy of hepatic and renal tumors as an image guidance modal-

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ity for the initial puncture and catheter insertion. Previously only CT or MRI fluoroscopy were used [11, 12].

In an initial exploratory analysis, it was shown that a majority of catheter placements for CT-guided HDR brachytherapy can be performed with sonography equipment additionally positioned adjacent to the CT table. The kidneys as well as the caudal liver segments (3/4B/5/6) appeared to be particularly suitable as sonographically-accessible regions; in the previous patient cohort only a few lesions in one of cranial liver segments (2/4A/7/8) were inaccessible. Here the results are in line with studies that, for example, have assessed the value of ultrasound and CT for radiofrequency ablation of hepatocellular carcinomas and which were able to document comparable results [9]. However, the benefits of CT fluoroscopy are also known when, similar to our cohort, certain regions of the abdomen are difficult for ultrasound to access [13, 14]. However, many percutaneous procedures in interventional radiology still lack a comparative, randomized study between sonography and CT fluoroscopy.

The significance of the study is primarily limited by the small number of patients on whom the possibilities of the novel technique was observed. The goal should now be to use a larger number of cases to define the value of ultrasound-assisted catheter placement for a practical implementation in CT-guided HDR brachytherapy. A suitable comparison criterion appears to be the reduction of fluoroscopy time during CT, which is proportional to the radiation exposure of the medical staff involved and could already be significantly reduced in the present study with the aid of ultrasound [15]. Similarly, the immediate availability of a second imaging modality improves the visibility and accessibility of certain lesions similar to the principle of CT / ultrasound image fusion [16]. Ultimately, this may result in improved positioning of the irradiation catheters or a reduction in the number needed for sufficient irradiation. For radiotherapy planning, however, CT imaging will continue to be required, and the procedure will therefore not be fully within the field of sonography.

Summary

Sonographically-assisted catheterization in interstitial HDR brachytherapy has the potential to reduce the use of CT fluoroscopy and therefore the radiation exposure of the interventional radiologist. The visibility of the target lesion in sonography is in some cases superior to CT fluoroscopy and allows accurate catheter placement even in previously operated patients.

The approaches gained from this study are intended to develop the concrete added value of the procedure in subsequent investigations on a larger group of patients.

CENTRAL STATEMENTS / CLINICAL RELEVANCE

- Ultrasound-assisted catheterization during CT-guided brachytherapy of abdominal tumors is technically feasible and safe.
- Ultrasound-based puncture can improve catheter placement.
- A significant reduction in fluoroscopy time can help reduce the radiation exposure of medical personnel.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Collettini F, Singh A, Schnapauff D et al. Computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of metastases adjacent to the liver hilum. Eur J Radiol 2013; 82: e509 – e514

[2] Yang W, Yan K, Wu GX et al. Radiofrequency ablation of hepatocellular carcinoma in difficult locations: Strategies and long-term outcomes. World J Gastroenterol 2015; 21: 1554 – 1566

[3] Lin ZY, Li GL, Chen J et al. Effect of heat sink on the recurrence of small malignant hepatic tumors after radiofrequency ablation. J Cancer Res Ther 2016; 12: C153 – C158

[4] Van den Begin R, Engels B, Gevaert T et al. Impact of inadequate respiratory motion management in SBRT for oligometastatic colorectal cancer. Radiother Oncol 2014; 113: 235 – 239

[5] Kloeckner R, dos SantosDP, Schneider J et al. Radiation exposure in CT-guided interventions. Eur J Radiol 2013; 82: 2253 – 2257

[6] Rogits B, Jungnickel K, Lowenthal D et al. Prospective Evaluation of the radiologist's hand dose in CT-guided interventions. Rofo 2013; 185: 1081 – 1088

[7] Gianfelice D, Lepanto L, Perreault P et al. Effect of the learning process on procedure times and radiation exposure for CT fluoroscopy-guided percutaneous biopsy procedures. J Vasc Interv Radiol 2000; 11: 1217 – 1221

[8] Schaefer PJ, Schaefer FKW, Heller M et al. CT fluoroscopy-guided biopsy of small pulmonary and upper abdominal lesions: Efficacy with a modified breathing technique. J Vasc Interv Radiol 2007; 18: 1241 – 1248

[9] Wu J, Chen P, Xie YG et al. Comparison of the effectiveness and safety of ultrasound- and CT-guided percutaneous radiofrequency ablation of non-operation hepatocellular carcinoma. Pathol Oncol Res 2015; 21: 637 – 642

[10] Sacks D, McClenny TE, Cardella JF et al. Society of Interventional Radiology clinical practice guidelines. J Vasc Interv Radiol 2003; 14: S199 – S202

[11] Collettini F, Lutter A, Schnapauff D et al. Unresectable colorectal liver metastases: percutaneous ablation using CT-guided high-dose-rate brachytherapy (CT-HDBRT). Rofo 2014; 186: 606 – 612

[12] Ricke J, Thormann M, Ludewig M et al. MR-guided liver tumor ablation employing open high-field 1. 0T MRI for image-guided brachytherapy. Eur Radiol 2010; 20: 1985 – 1993

[13] Sheafor DH, Paulson EK, Kliewer MA et al. Comparison of sonographic and CT guidance techniques: does CT fluoroscopy decrease procedure time? Am J Roentgenol 2000; 174: 939 – 942

[14] Mukhtar KN, Mahmood SN, Umair SF. CT guided percutaneous renal biopsy versus ultrasound guided for obtaining adequate tissue. J Pak Med Assoc 2012; 62: 880 – 882

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[15] Rathmann N, Haeusler U, Diezler P et al. Evaluation of radiation exposure of medical staff during CT-guided interventions. J Am Coll Radiol 2015; 12: 82 – 89

[16] Lee MW, Rhim H, Cha DI et al. Planning US for percutaneous radiofrequency ablation of small hepatocellular carcinomas (1–3 cm): value of fusion imaging with conventional US and CT/MR images. J Vasc Interv Radiol 2013; 24: 958 – 965

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Veröffentlichung 13

Biliary duct stenosis after image-guided high-dose-rate interstitial brachytherapy of central and hilar liver tumors : A systematic analysis of 102 cases.

Powerski M, Penzlin S, Hass P, Seidensticker R, Mohnike K, **Damm R**, Steffen I, Pech M, Gademann G, Ricke J, Seidensticker M.

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ORIGINAL ARTICLE

Biliary duct stenosis after image-guided high-dose-rate interstitial brachytherapy of central and hilar liver tumors

A systematic analysis of 102 cases

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Abstract

Objective Image-guided high-dose-rate interstitial brachytherapy (iBT) with iridium-192 is an effective treatment option for patients with liver malignancies. Little is known about long-term radiation effects on the bile duct system when central hepatic structures are exposed to iBT. This retrospective analysis investigates the occurrence of posthepatic cholestasis (PHC) and associated complications in patients undergoing iBT.

Materials and methods We identified patients who underwent iBT of hepatic malignancies and had point doses of ≥1 Gy to central bile duct structures. Patients with known bile duct-related diseases or prior bile duct manipulation were excluded.

Results 102 patients were retrospectively included. Twenty-two patients (22%) developed morphologic PHC after a median of 17 (3–54) months; 18 of them were treated using percutaneous transhepatic cholangiopancreatography drainage or endoscopic retrograde cholangiopancreatography. The median point dose was 24.8 (4.4–80) Gy in patients with PHC versus 14.2 (1.8–61.7) Gy in those without PHC ($p = 0.028$). A dose of 20.8 Gy (biological effective dose, $BED_{3/10} = 165/64.1$ Gy) was identified to be the optimal cutoff dose ($p = 0.028$; 59% sensitivity, 24% specificity). Abscess/cholangitis was more common in patients with PHC compared to those without (4 of 22 vs. 2 of 80; $p = 0.029$). Median survival did not differ between patients with and without PHC (43 vs. 36 months; $p = 0.571$).

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Conclusion iBT of liver malignancies located near the hilum can cause PHC when the central bile ducts are exposed to high point doses. Given the long latency and absence of impact of iBT-induced PHC on median survival, the rate of cholestasis and complications seen in our patients appears to be acceptable.

Keywords Local ablation · Interstitial brachytherapy · Bile duct stenosis · Extrahepatic cholestasis · Central and hilar liver tumors

Gallengangstenosen nach bildgeführter interstitieller Hochdosis-Brachytherapie zentraler und hilusnaher Lebertumore

Eine systematische Analyse von 102 Fällen

Zusammenfassung

Zielsetzung Die bildgestützte interstitielle Hochdosis-Brachytherapie (iBT) mit Iridium-192 ist eine effektive Methode zur Ablation hepatischer Malignome. Unklar ist die Langzeitauswirkung auf das Gallengangsystem bei Bestrahlung zentraler Leberstrukturen. Die vorgestellte retrospektive Studie eruiert den Einfluss der iBT auf die Entstehung posthepatischer Cholestasen (PHC) und vergesellschafteter Komplikationen.

Material und Methoden Eingeschlossen wurden Patienten mit iBT hepatischer/hilusnaher Malignome mit Punktdosen ≥1 Gy an zentralen Gallengangstrukturen. Ausschlusskriterien waren gallengangassoziierte Erkrankungen oder vorherige Manipulationen an den Gallenwegen.

Ergebnisse In die Studie konnten 102 Patienten eingeschlossen werden. Von diesen entwickelten 22 (22 %) nach im Median 17 Monaten (Spanne 3–54 Monate) eine morphologische PHC, die in 18 Fällen (18 %) mit perkutaner transhepatischer Cholangiodrainage oder endoskopischer retrograder Cholangiopankreatikographie abgeleitet werden musste. Die Punktdosis der Patienten mit PHC lag im Median bei 24,8 Gy (Spanne 4,4–80 Gy), derjenigen ohne PHC bei 14,2 Gy (Spanne 1,8–61,7 Gy; $p = 0{,}028$). Bei 20,8 Gy (biologische effektive Dosis, $BED_{3/10} = 165/64{,}1$ Gy) konnte ein optimaler Cut-off-Wert (Schwellendosis) ermittelt werden ($p = 0{,}028$; Sensitivität 59 %, Spezifität 24 %). Abszesse/Cholangitiden traten bei Patienten mit PHC signifikant häufiger auf als ohne (4 von 22 vs. 2 von 80; $p = 0{,}029$). Im medianen Überleben zwischen Patienten mit und ohne PHC zeigte sich kein Unterschied (43 vs. 36 Monate; $p = 0{,}571$).

Schlussfolgerung Die iBT hilusnaher Lebertumore kann bei hohen Punktdosen an zentralen Gallengängen zu einer klinisch relevanten PHC führen. In Anbetracht der langen Latenzzeit und der fehlenden Auswirkung iBT-assoziierter PHC auf das mediane Überleben halten wir die ermittelte Rate an Strikturen und Komplikationen für akzeptabel.

Schlüsselwörter Lokale Ablation · Interstitielle Brachytherapie · Gallangangsstenose · Extrahepatische Cholestase · Zentrale und hilusnahe Lebertumore

Introduction

Treatment of hepatic malignancies located centrally or near the hilum continues to be a clinical challenge regardless of the tumor entity [1, 2]. The natural history of such lesions is characterized by obstructive bile duct complications and reduced overall survival [3]. For most types of malignant liver lesion, the effect of systemic treatments is moderate and/or short. Moreover, for technical, oncologic, or medical reasons, most patients with central or hilar liver tumors are not candidates for surgery [1–4]. Local thermal ablation techniques such as radiofrequency ablation (RFA) or microwave ablation are limited by reduced effectiveness due to the heat-sink effect near large blood vessels in the hilar region and a high rate of bile duct-related complications (up to 46%) [5, 6]. Other thermal approaches such as cryoablation, while having low biliary toxicity in animal experiments, have been shown to achieve only moderate local tumor control in the clinical setting [7, 8].

Radiotherapy, applied either percutaneously or interstitially (as catheter-based radiotherapy, iBT), has evolved into an effective and also safe local therapy for central liver tumors [9, 10]. Safety data derive mainly from theoretic estimates and observational case series [11]. However, there is evidence of varying strength to support the assumption that even significant radiation exposure will not have an effect on the main bile ducts: Collettini et al. reported one biliary complication (biliary abscess in a pancreatic cancer patient with hepaticojejunostomy) after catheter-based radiotherapy of 34 central liver metastases from various primaries (target dose of 15–20 Gy) located within 5 mm of the common bile duct or hepatic bifurcation. A remarkable local control rate of 88.2% was achieved during a mean follow-up of 18.75 months [9]. Comparable results were

published by Ricke et al. after catheter-based radiotherapy of 20 central lesions in unfavorable location for RFA. They achieved a local control rate of up to 93% after 12 months and saw only one biliary complication (transient obstructive jaundice) [10]. Data on radiation exposure of the main bile ducts were not provided in these two studies. Studies of percutaneous radiotherapy of liver tumors typically focus on efficacy and rarely investigate the relationship between radiation exposure and biliary duct complications. Two studies of hepatobiliary adverse events after stereotactic body radiation therapy (SBRT) reported an overall rate of 18.8–26% of ≥ grade 3 toxicities according to CTCAE v4.03 [12] (including lab values) for the treatment of hepatic tumors in any location. Unfortunately, these studies did not provide satisfactory data on dose-related bile duct vulnerability [13, 14].

To the best of our knowledge, systematic clinical trials including dosimetric analysis of the radiation sensitivity of central bile ducts are currently not available. Therefore, we retrospectively identified 102 patients who underwent image-guided high-dose-rate interstitial brachytherapy (iBT) for liver malignancies located centrally or near the hilum to systematically analyze the occurrence of stenotic cholestasis and related complications and the impact on outcome and survival. The aim was to identify a safe cutoff dose for radiation exposure of biliary structures. To allow comparison of the doses identified in our study with doses published for fractionated radiotherapy regimens, we converted relevant doses to biological effective doses (BED) using the linear quadratic formula published by Fowler in 1989 [15, 16].

Materials and methods

Patient population

Patients who underwent image-guided high-dose-rate interstitial brachytherapy (iBT) of hepatic malignancies located centrally or near the hilum were retrospectively identified for inclusion in this retrospective analysis when they had a point dose of at least 1 Gy to a central bile duct. For the purpose of this analysis, the central bile ducts included all bile ducts that were clearly visible in computed tomography (CT) and magnetic resonance imaging (MRI) datasets obtained before radiotherapy for diagnosis and planning (common hepatic duct [CHD], left and right bile duct, and visible first-order branches). Exclusion criteria were bile duct malignancy, cancer of unknown primary (CUP) syndrome, primary sclerosing/chronic cholangitis, and status post biliary manipulation (liver transplant, papillary splitting, bile duct stenting, biliodigestive anastomosis), prior radiotherapy of the liver, no follow-up, and low point dose

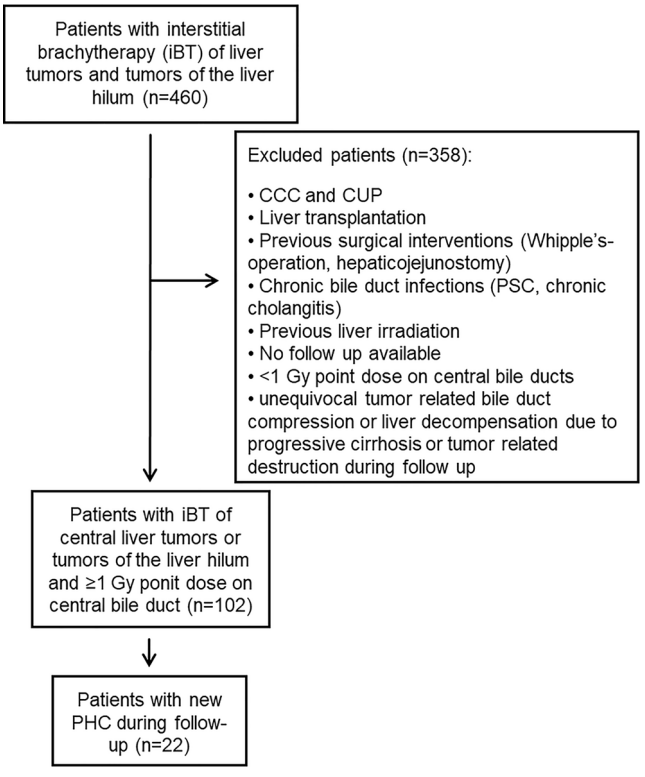

Fig. 1 Consort diagram of inclusion and exclusion criteria and the final study population. *CCC* cholangiocellular carcinoma, *CUP* cancer of unknown primary, *PSC* primary sclerosing cholangitis, *PHC* post-hepatic cholestasis

of <1 Gy to central bile ducts (Fig. 1). The indication for iBT was established by an interdisciplinary tumor board. Criteria were nonresectable malignant liver lesion (unfavorable location, poor liver function, small liver remnant), medical/oncologic contraindication to surgery, and patient refusal of surgery. Our retrospective analysis was approved by the local ethics committee.

Intervention/iBT catheter placement

The technique of image-guided placement of the catheters for iBT has been described before [17, 18]. In brief, the catheters were placed using CT fluoroscopy (Aquilion Prime, Toshiba, Japan) or in an open MRI scanner (1.0 T Panorama HFO, Philips Healthcare, Best, The Netherlands). Following puncture of the target lesion with an 18-G coaxial needle, a stiff angiography wire (Amplatz, Boston Scientific, Boston, MA, USA, for CT interventions or Radiofocus Guide Wire Stiff Type, Terum, Tokyo, Japan, for MR interventions) was introduced for placement of a 6-F introducer sheath (Radiofocus, Terumo) in Seldinger technique, through which the brachytherapy catheter (Nucletron, Elektra AB, Stockholm, Sweden) was inserted. For radiotherapy planning, catheter placement was followed by

contrast-enhanced CT (Immeron 300, Braco, Milano, Italy; 2 ml/kg body weight, maximum dose of 150 ml, delay of 120s, 3 mm slice thickness) or MRI (T1-weighted 3D turbo field echo sequences). Sedation, analgesia, and monitoring of the patients and removal of brachytherapy catheters were performed as described by Ricke et al. [17].

Radiation properties, treatment planning

Radiotherapy was planned using Oncentra software (Nucletron, Elektra AB, Stockholm, Sweden). First, the clinical target volume was delineated in the planning CT/MRI dataset in a slice-by-slice fashion. Next, the relative coordinates (x, y, z) of the catheter tips in relation to the tumor margin were transferred to the planning system. The anticipated minimum D99.9 per clinical target volume was a single dose of 15–25 Gy, depending on the tumor type [19, 20], and was adjusted to spare structures at risk (threshold dose of 15 Gy/ml for stomach and duodenum) [21]. The high-dose-rate (HDR) afterloading system used in our study (Nucletron, Elektra AB, Stockholm, Sweden) has an iridium-192 source with a nominal activity of 10 Ci. To identify patients eligible for our analysis, we outlined the contours of the central bile ducts (i. e., ducts clearly visible on pretherapeutic and planning imaging) and the Oncentra software calculated the maximum bile duct point dose (Gy) for each individual. To ensure comparability with published data, doses are additionally provided as biological effective doses (BED), which were calculated using the linear square model [15, 16]. BED were calculated for $\alpha/\beta = 3$ (late-responding tissues, abbreviated to BED_3) and $\alpha/\beta = 10$ (early-responding tissues, abbreviated to BED_{10}).

Follow-up

After iBT, all patients underwent follow-up MRI of the liver at 3-month intervals. Minimum requirement for the MRI protocol included T2-weighted sequences with and without fat saturation, T1-weighted sequences before and during gadolinium contrast agent administration (dynamic sequences), and—if performed at our hospital—T1-weighted sequences acquired 20 min after IV administration of 0.1 ml/kg Gd-EOB-DTPA (Primovist, Bayer, Leverkusen, Germany). Patients with contraindications to MRI underwent abdominal CT scans with three-phase liver imaging after IV contrast (at our hospital: Imeron 300; 2 ml/kg, maximum dose of 150 ml; Bracco, Milan, Italy) administration. In addition, follow-up included clinical examinations with documentation of adverse effects, serology, hematology, and liver function parameters: aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AL), gamma-glutamyltransferase (GGT), bilirubin, albumin, and clotting.

Definition of posthepatic cholestasis

New-onset posthepatic cholestasis was diagnosed when there was bile duct dilatation peripheral to the site of maximum radiation exposure. Dilatation was assumed when the bile duct diameter was over 5 mm or when there was an increase in diameter of at least 2 mm on follow-up CT or MRI compared with the pretherapeutic diameter. Patients with a concomitant first-time bilirubin level above 21 µmol/l (>1.2 mg/dl) were treated using percutaneous transhepatic cholangiopancreatography drainage/endoscopic retrograde cholangiopancreatography (PTCD/ERCP). Patients with disease progression leading to unequivocal tumor-related bile duct compression as well as patients with liver decompensation (e. g., due to progressive cirrhosis or tumor-related liver parenchyma destruction) were secondarily excluded from the analysis.

Statistical analysis

All study data were compiled retrospectively. Statistical analysis was performed using SPSS version 24 (IBM, Armonk, NY, USA). The group comparisons presented in Table 1 were conducted using either Fischer's exact test, the U test, or the log-rank test. The Kaplan–Meier method was used to calculate overall survival rates. Receiver operating characteristic (ROC) curve analysis was performed to identify an optimal radiation dose cutoff. Statistical significance was assumed at p-values <0.05.

Results

We identified 460 patients who underwent iBT of primary or secondary liver malignancies at our department from 2007 through 2014; 102 of them met our criteria and were included in this retrospective analysis (Fig. 1 and Materials and Methods). Median follow-up of all enrolled individuals was 31 months (range 3–69). Twenty-two patients (22%) developed PHC distal to radiation-exposed bile ducts after a median of 17 months (range 3–54). In these 22 patients, PHC was apparent on CT or MRI, and 18 of them had increased bilirubin levels and underwent PTCD or ERCP for drainage of bile (Table 1). Fig. 2 shows an example of PHC after iBT of metastatic lymph nodes near the hilum.

There were six instances of abscess or cholangitis in the total study population (6%). This complication was significantly more common in patients with PHC than in those without (4 of 22 [18%] vs. 2 of 80 [3%]; $p = 0.029$). No effect of PHC or its complications on median survival (43_{PHC} vs. $36_{no\ PHC}$ months; $p = 0.571$) or on the course of survival curves (Fig. 3) was noted.

Table 1 Patients with iBT of central liver tumors and tumors of the liver hilum

	Enrolled patients, $n = 102$		*p*-value
	PHC during follow-up $n = 22$ (22%)	No PHC during follow-up $n = 80$ (78%)	
Male/female (*n*)	11/11	50/30	0.689
Age (years; median; range)	69 (50–84)	66 (35–89)	0.625
Tumor entity (n)			
Colorectal cancer	11	36	0.834
Hepatocellular carcinoma	4	25	0.437
Breast cancer	2	12	0.731
Other ($n \leq 3$)	5	7	0.152
Liver (n)			
Steatosis	3	5	0.379
Cirrhosis	5	22	1.000
Cholecystectomy	12	19	0.064
Bilirubin (µmol/l) before iBT[a]	8.1 (4.9–30.9)	7.9 (2.8–40.4)	0.935
Additional treatment (n)			
Previous chemotherapy	18	53	0.586
Chemotherapy during FU	12	43	1.000
Ablation/Embolization during FU	3	17	0.763
Dosimetric calculation (Gy)			
Point dose[a]	24.8 (4.4–80)	14.2 (1.8–61.7)	*0.028
Point dose BED_3[a,b]	229.8 (10.9–2213.3)	81.4 (2.9–1330.7)	n.a.
Point dose BED_{10}[a,b]	86.3 (6.3–720)	34.4 (2.1–442.4)	n.a.
Optimal cutoff	20.8	–	–
Optimal cutoff BED_3[b]	165	–	–
Optimal cutoff BED_{10}[b]	64.1	–	–
Further characteristics			
Follow-up after iBT (months)[a]	31 (3–69)	26 (3–73)	0.456
Time between iBT and PHC (months)[a]	17 (3–54)	–	–
PHC in CT/MRI only (*n*)	4 (18%)	–	–
PHC requiring ERCP/PTCD (*n*)	18 (82%)	–	–
Bilirubin when PHC was detected (µmol/l)[a]	42.7 (4.7–370.8)	–	–
Abscess/cholangitis (*n*)	4 (18%)	2 (3%)	*0.029
Median survival (month)	43	36	0.571

[a]median (range)
[b]calculated dose
*statistically significant *p*-value
PHC posthepatic cholestasis, *CT* computed tomography, *MRI* magnetic resonance imaging, *ERCP* endoscopic retrograde cholangiopancreatography, *PTCD* percutaneous transhepatic cholangiography drainage, *BED* biological effective dose, BED_3 BED calculation for $\alpha/\beta = 3$ (late responding tissues), BED_{10} BED calculation for $\alpha/\beta = 10$ (early responding tissues)

The median point dose to central bile ducts was 24.8 (4.4–80) Gy in patients with PHC versus 14.2 (1.8–61.7) Gy in those without PHC ($p = 0.028$; see Table 1 for BED). ROC analysis ($p = 0.028$) identified 20.8 Gy as the optimal cutoff ($BED_{3/10} = 165/64.1$ Gy; 59% sensitivity, 24% specificity; Fig. 4).

Comparability of the two groups was tested for sex, age, liver disease, gallbladder resection, baseline bilirubin level, and prior ablation and systemic therapies: no significant differences were identified (Table 1).

Discussion

The results presented here suggest that the risk of radiation-induced bile duct stenosis increases with the point dose to which structures-at-risk are exposed. In our analysis, patients who developed cholestasis after iBT had a significantly higher point dose exposure of central bile ducts than patients without PHC. Nevertheless, there is scatter and overlap in point doses between the two groups, resulting in poor discriminatory power despite a significant area under the curve (AUC) in ROC analysis. The best

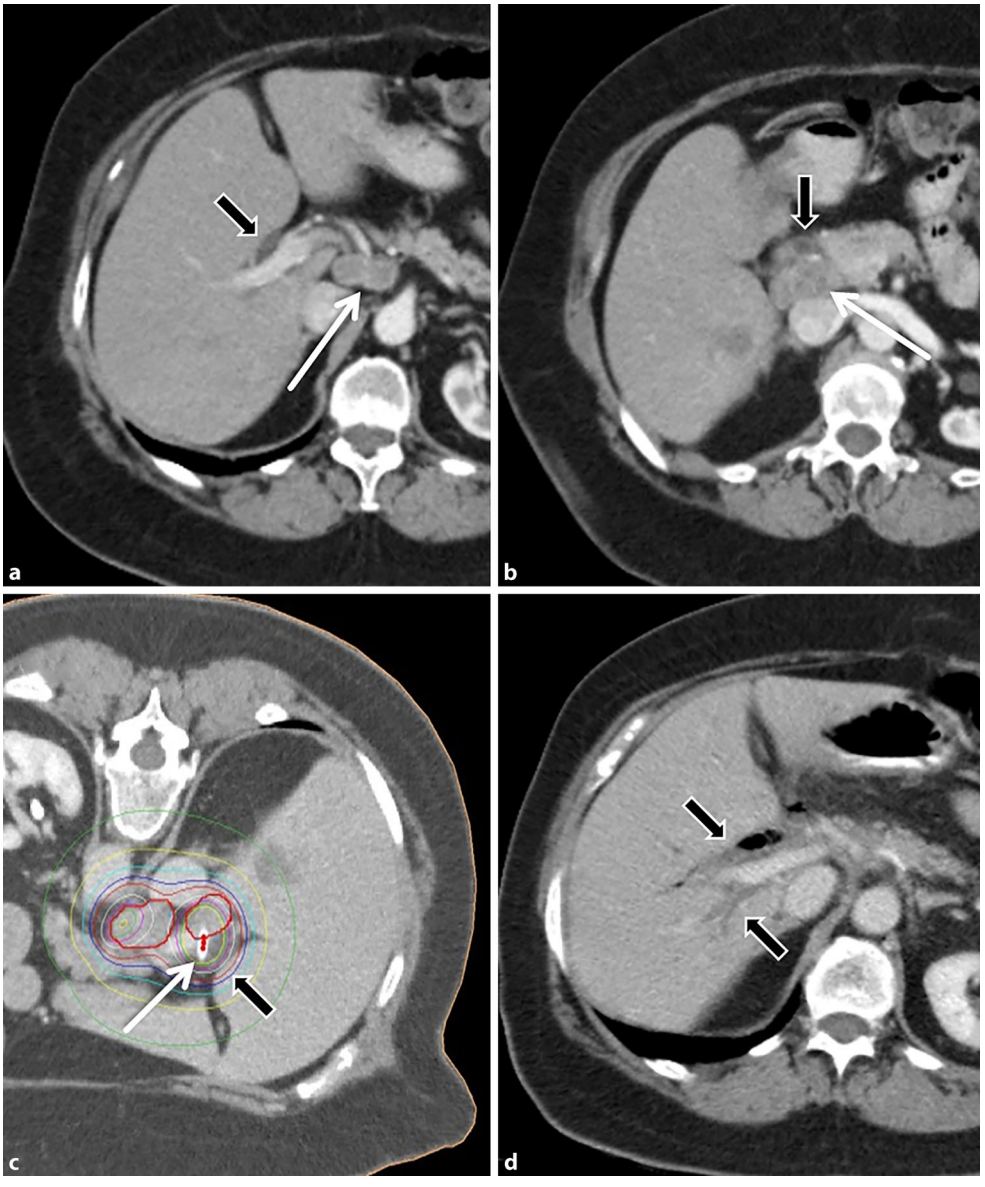

Fig. 2 Example of posthepatic cholestasis after image-guided high-dose-rate interstitial brachytherapy (iBT). **a**, **b** *Black arrows* indicate the course of the right bile duct (**a**) and of the choledochal duct (**b**). *White arrows* indicate lymph node metastases from colorectal cancer with hepatic metastatic spread. **c** Irradiation planning with isodoses. Brachytherapy catheters were advanced into the lymph nodes (*white arrow*) with the patient in prone position. The 25 Gy isodose cuts across the right bile duct (*black arrow*). **d** 12 months after iBT, the patient developed right-hepatic cholestasis (*black arrows*) which was successfully treated by endoscopic retrograde cholangiopancreaticography and metal stent placement (aerobilia)

cutoff (threshold dose) based on our results turned out to be 20.8 Gy ($BED_{3/10}$ = 165/64.1 Gy); however, this cutoff has only 59% sensitivity, and 41% of patients with PHC had a dose below 20.8 Gy. Calculations predict that if the threshold dose identified here is not exceeded, the rather high PHC rate of 22% should drop to approximately 9%. While only few data are available in the literature on biliary dosimetry, the available data at least allow a plausibility check of the threshold dose identified in our analysis. Tselis et al. treated 59 central liver tumors in 41 patients using iBT [22]. The total dose was applied in four fractions (4 × 8 Gy=32 Gy; $BED_{3/10}$ = 117.3/57.6 Gy; 19 patients) or as a single dose (1 × 14 Gy; $BED_{3/10}$ = 79.3/33.6 Gy, 22 patients). No biliary toxicity was observed by Tselis et al. during a median follow-up period of 12.4 months. In a study of 50 patients who underwent stereotactic body radiation therapy (SBRT), Eriguchi et al. reported one case of cholestasis 12 months after the last radiotherapy session [23]. In this patient, overlapping fields in metachronic treatment of two lesions, each with 5 × 8 Gy = 40 Gy, resulted in a total dose of 10 × 8 Gy = 80 Gy ($BED_{3/10}$ = 293.33/144 Gy) in the area where the patient later developed bile duct stenosis. None of the 14 patients with a biliary dose of 5 × 8 Gy = 40 Gy ($BED_{3/10}$ = 146.7/72 Gy) or any of the remaining patients with lower doses developed any symptoms during a median follow-up period of 18.2 months. The results of both studies allow derivation of presumably safe dose levels (Tselis et al.: $BED_{3/10}$ = 117.3/57.6 Gy; Erigutchi et al.: $BED_{3/10}$ = 146.7/72 Gy—no PHC in either study) for the central bile ducts which are approximately on the order of the cutoff identified in our study ($BED_{3/10}$ = 165/64.1 Gy; 9 PHC in 102 patients). The fact that no cholestasis was

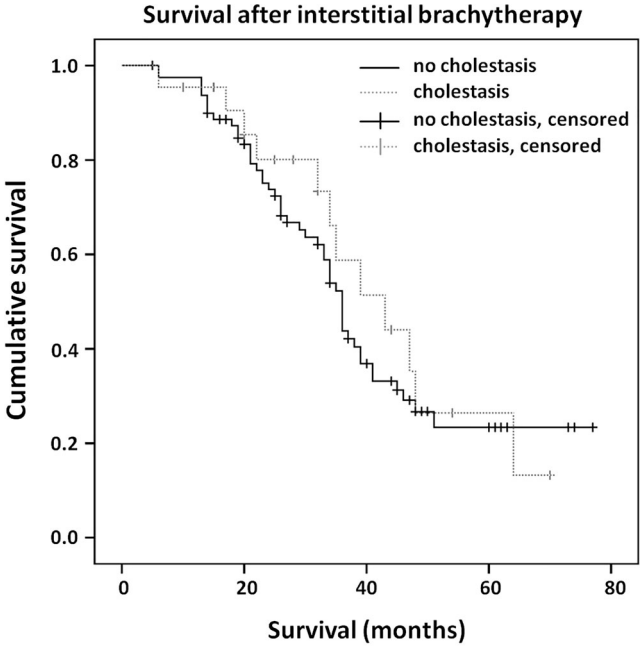

Fig. 3 Comparison of survival curves of patients with posthepatic cholestasis (PHC; *interrupted gray line*; $n=22$) and patients without PHC (*black line*; $n=80$) following image-guided high-dose-rate brachytherapy of central or hilar malignant liver lesions ($p=0.571$)

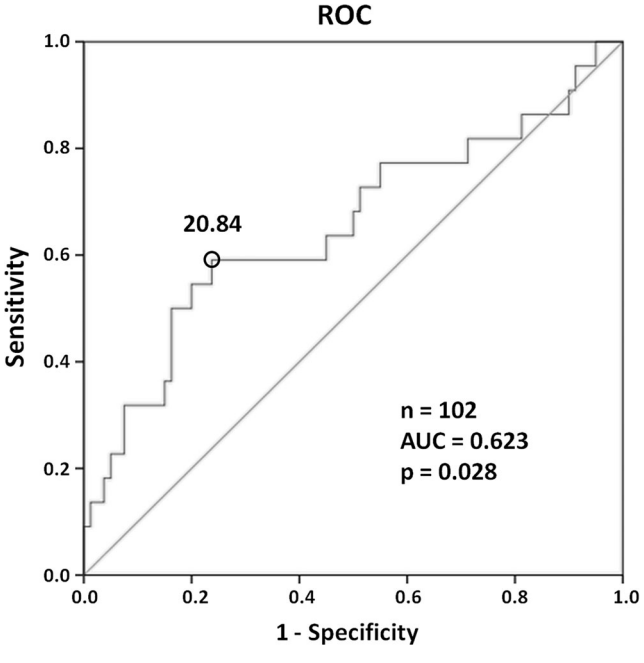

Fig. 4 Receiver operating characteristic (ROC) curve analysis for determining the optimal cutoff dose (in Gy) tolerated by the central bile ducts without the risk of inducing cholestasis. *AUC* area under the curve

observed by either Tselis et al. or Eriguchi et al. might be attributable to the short follow-up (12.4 and 18.2 months, respectively), especially in light of the observation that it took a median of 17 months (range 3–54) before bile duct stenoses occurred in our patient population. Overall, though, we think that the results derived from the two studies just quoted are consistent with the threshold dose determined in our study, at the same time confirming that our dose is plausible. Threshold dose volumes of the central biliary tract after SBRT were also evaluated by Osmundson et al. and Toesca et al. [13, 14]. However, these investigators primarily assessed the predictive power of dose exposure for the occurrence of hepatobiliary grade 2+ and 3+ toxicity, and their data say little about the radiation vulnerability of central bile ducts. Osmundson et al., for instance, show that irradiation of an area >21 cm^3 with 72 Gy_{BED10} or of >24 cm^3 with 66 Gy_{BED10} of a volume defined as the central biliary tract significantly increases the likelihood of grade 3+ hepatobiliary toxicities. It is not clear from the article how many instances of toxicity were attributable to obstructive cholestasis developing in patients with radiation doses above this threshold. Moreover, the 13 PHCs in the 96 study patients were nearly exclusively observed in patients with cholangiocellular carcinoma (11 PHC in 20 CCA patients). In these cases, PHC may not be attributable to radiation damage alone.

Biliary congestion is among the most common causes of spontaneous cholangitis and biliogenic abscess [24]. The results in our population are consistent with this pathomechanism, as we typically observed complications in patients with PHC. Rapid management of cholestasis (ERCP/PTCD plus stenting as needed), IV antibiotic treatment, and transcutaneous abscess drainage are the therapeutic measures of first choice and can reduce the mortality rate of acute cholangitis far below 5% [25]. This explains the absence of a difference in median survival or the total survival curve between patients with and without PHC in our population (Fig. 3). The fact that it takes a median of 17 months before bile duct stenosis becomes apparent has important implications in a population mostly including patients with a reduced life expectancy due to their underlying conditions such as hepatocellular (HCC) and colorectal cancer (CRC). Patients with HCC considered for ablation generally have a poor BCLC A or good BCLC B stage of disease, with a median survival of 20 to 60 months [26]. Patients with hepatic metastasis from CRC are typically awaiting second- or third-line chemotherapy and have a median survival of approximately 11 months [27]. Thus, the remaining life expectancy, in conjunction with the radiosensitivity of the target lesions in the liver (HCC: local control >90% after >12 months for iBT with 15 Gy [20]; CRC: >80% local control after >40 months for irradiation with 25 Gy [19]), justifies the application of an ablative radiation dose

in most cases. For instance, when the dose of D100 15 Gy is adhered to in patients with HCC, only poor catheter positioning will lead to point doses to the bile ducts that exceed the threshold dose of 20.8 Gy identified here. Options in patients with central metastasis from CRC include administration of a lower dose (local control on the order of 60–80% for 20 Gy after 12 months [19]) and/or use of more ablation catheters to achieve a steeper decrease in dose at the border. Furthermore, it should be noted that for selected cases, a fractionated regime can be considered (to reduce BED_3), were ablation catheters stay in place and irradiation is repeated, e. g., twice a day. However, this demands a strict organization and a great amount of discipline from the patient to lay still for a time span of 1–2 days (2–4 fractions). When life expectancy is shorter than the time it takes for stenotic complications to develop, the biliary threshold dose can be ignored. Consequently, the overall clinical situation must be considered to decide on the best approach for each patient. Finally, it should be pointed out here that despite high bile duct exposure in some of the patients and related complications in our study population, median overall survival was high at 43 months with PHC and 36 months without PHC. Such survival rates are difficult to achieve without local ablation, given the mechanical complications (portal vein and bile duct compression) facing patients with central liver tumors.

Our study has some limitations including the retrospective design and the fact that it is a single-center analysis. The threshold dose we determined here might be affected, for example, by scar formation with bile duct narrowing following iatrogenic injury of the bile ducts during ablation catheter placement. Note also that we did not include patients with cholangiocellular carcinoma and/or chronic bile duct disease (or chronic pathogen colonization of bile ducts after surgical or other medical manipulation). Therefore, it remains open whether our results also apply in patients with prior damage or diseases of the bile ducts.

Conclusion

In conclusion, our findings suggest that in most patients, the radiation sensitivity of central bile ducts does not limit image-guided interstitial high-dose-rate brachytherapy of malignant liver lesions located centrally or in the hilar area. While there is a dose-dependent vulnerability of central bile ducts, the threshold dose identified in our analysis is high, and there is a long median interval before patients are likely to develop posthepatic cholestasis. In addition, with adequate laboratory and radiologic follow-up and timely intervention, bile duct-related complications have no effect on median survival.

Conflict of interest M. Powerski, S. Penzlin, P. Hass, R. Seidensticker, K. Mohnike, R. Damm, I. Steffen, M. Pech, G. Gademann, J. Ricke, and M. Seidensticker declare that they have no competing interests.

References

1. Kuo I-M, Huang S-F, Chiang J-M et al (2015) Clinical features and prognosis in hepatectomy for colorectal cancer with centrally located liver metastasis. World J Surg Oncol 13:92. https://doi.org/10.1186/s12957-015-0497-6
2. Schmoll HJ, Van Cutsem E, Stein A et al (2012) ESMO consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol 23:2479–2516. https://doi.org/10.1093/annonc/mds236
3. Fukasawa M, Takano S, Shindo H et al (2017) Endoscopic biliary stenting for unresectable malignant hilar obstruction. Clin J Gastroenterol 10:485–490. https://doi.org/10.1007/s12328-017-0778-4
4. Cho Y, Kim TH, Seong J (2017) Improved oncologic outcome with chemoradiotherapy followed by surgery in unresectable intrahepatic cholangiocarcinoma. Strahlenther Onkol 193:620–629. https://doi.org/10.1007/s00066-017-1128-7
5. Kim Y, Rhim H, Cho OK et al (2006) Intrahepatic recurrence after percutaneous radiofrequency ablation of hepatocellular carcinoma: analysis of the pattern and risk factors. Eur J Radiol 59:432–441. https://doi.org/10.1016/j.ejrad.2006.03.007
6. Ohnishi T, Yasuda I, Nishigaki Y et al (2008) Intraductal chilled saline perfusion to prevent bile duct injury during percutaneous radiofrequency ablation for hepatocellular carcinoma. J Gastroenterol Hepatol 23:e410–e415. https://doi.org/10.1111/j.1440-1746.2007.05091.x
7. Kahlenberg MS, Volpe C, Klippenstein DL et al (1998) Clinicopathologic effects of cryotherapy on hepatic vessels and bile ducts in a porcine model. Ann Surg Oncol 5:713–718
8. Huang Y-Z, Zhou S-C, Zhou H, Tong M (2013) Radiofrequency ablation versus cryosurgery ablation for hepatocellular carcinoma: a meta-analysis. Hepatogastroenterology 60:1131–1135. https://doi.org/10.5754/hge121142
9. Collettini F, Singh A, Schnapauff D et al (2013) Computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of metastases adjacent to the liver hilum. Eur J Radiol 82:e509–e514. https://doi.org/10.1016/j.ejrad.2013.04.046
10. Ricke J, Wust P, Wieners G et al (2004) Liver malignancies: CT-guided interstitial brachytherapy in patients with unfavorable lesions for thermal ablation. J Vasc Interv Radiol 15:1279–1286. https://doi.org/10.1097/01.RVI.0000141343.43441.06
11. Grimm J, LaCouture T, Croce R et al (2011) Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy. J Appl Clin Med Phys 12:3368
12. National Cancer Institute (2009) CTCAE v4.03. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. Accessed 17 July 2018
13. Osmundson EC, Wu Y, Luxton G et al (2015) Predictors of toxicity associated with stereotactic body radiation therapy to the central hepatobiliary tract. Int J Radiat Oncol Biol Phys 91:986–994. https://doi.org/10.1016/j.ijrobp.2014.11.028
14. Toesca DAS, Osmundson EC, von Eyben R et al (2017) Central liver toxicity after SBRT: an expanded analysis and predictive nomogram. Radiother Oncol 122:130–136. https://doi.org/10.1016/j.radonc.2016.10.024
15. EQD2 and BED calculator. http://eqd2.com. Accessed 17 July 2018
16. Fowler JF (1989) The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 62:679–694. https://doi.org/10.1259/0007-1285-62-740-679

17. Ricke J, Wust P, Stohlmann A et al (2004) CT-guided brachytherapy. A novel percutaneous technique for interstitial ablation of liver metastases. Strahlenther Onkol 180:274–280. https://doi.org/10.1007/s00066-004-1179-4
18. Mohnike K, Neumann K, Hass P et al (2017) Radioablation of adrenal gland malignomas with interstitial high-dose-rate brachytherapy : efficacy and outcome. Strahlenther Onkol 193:612–619. https://doi.org/10.1007/s00066-017-1120-2
19. Ricke J, Mohnike K, Pech M et al (2010) Local response and impact on survival after local ablation of liver metastases from colorectal carcinoma by computed tomography-guided high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 78:479–485. https://doi.org/10.1016/j.ijrobp.2009.09.026
20. Mohnike K, Wieners G, Schwartz F et al (2010) Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: safety, efficacy, and effect on survival. Int J Radiat Oncol Biol Phys 78:172–179. https://doi.org/10.1016/j.ijrobp.2009.07.1700
21. Streitparth F, Pech M, Böhmig M et al (2006) In vivo assessment of the gastric mucosal tolerance dose after single fraction, small volume irradiation of liver malignancies by computed tomography-guided, high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 65:1479–1486. https://doi.org/10.1016/j.ijrobp.2006.02.052
22. Tselis N, Chatzikonstantinou G, Kolotas C et al (2013) Computed tomography-guided interstitial high dose rate brachytherapy for centrally located liver tumours: a single institution study. Eur Radiol 23:2264–2270. https://doi.org/10.1007/s00330-013-2816-z
23. Eriguchi T, Takeda A, Sanuki N et al (2013) Acceptable toxicity after stereotactic body radiation therapy for liver tumors adjacent to the central biliary system. Int J Radiat Oncol Biol Phys 85:1006–1011. https://doi.org/10.1016/j.ijrobp.2012.09.012
24. Ahmed M (2018) Acute cholangitis—an update. World J Gastrointest Pathophysiol 9:1–7. https://doi.org/10.4291/wjgp.v9.i1.1
25. Sun Z, Zhu Y, Zhu B et al (2016) Controversy and progress for treatment of acute cholangitis after Tokyo Guidelines (TG13). Biosci Trends 10:22–26. https://doi.org/10.5582/bst.2016.01033
26. Llovet JM, Brú C, Bruix J (1999) Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 19:329–338. https://doi.org/10.1055/s-2007-1007122
27. Bennouna J, Sastre J, Arnold D et al (2013) Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol 14:29–37. https://doi.org/10.1016/S1470-2045(12)70477-1

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Image-guided interstitial high-dose-rate brachytherapy in the treatment of metastatic esophageal squamous cell carcinoma.

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Original paper

Image-guided interstitial high-dose-rate brachytherapy in the treatment of metastatic esophageal squamous cell carcinoma

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Abstract

Purpose: To evaluate the efficacy of computed tomography (CT)- and magnetic resonance imaging (MRI)-guided interstitial high-dose-rate brachytherapy (HDR IBT = IBT) in patients with metastatic esophageal squamous cell carcinoma.

Material and methods: Eleven patients with 21 unresectable metastases of histologically proven esophageal squamous cell carcinoma were included in this retrospective study. Fourteen visceral and 7 lung metastases were treated with image-guided (CT or open MRI guidance) IBT using a ^{192}Iridium source (single fraction irradiation). Clinical and imaging follow-up were performed every 3 months after treatment. Primary endpoint was local tumor control (LTC) and safety. Furthermore, we analyzed safety, progression-free survival (PFS), and overall survival (OS).

Results: The median diameter of the target lesions was 2.2 cm (range: 0.7-6.8 cm), treated with a median D_{100} of 20.1 Gy (range: 10-25 Gy). During a median follow-up of 6.3 months (range: 3-21.8 months), three patients displayed local recurrences, resulting in LTC of 85.7%. Median PFS was 3.4 months and median OS after IBT was 13.7 months. No severe adverse events (grade 3+) requiring hospitalization or invasive intervention were recorded.

Conclusions: Image-guided IBT is a safe and effective treatment in patients with metastasized esophageal squamous cell carcinoma.

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Key words: esophageal cancer, image-guided intervention, interventional oncology, interstitial brachytherapy, metastases.

Purpose

Esophageal cancer (EC) is the eighth most common cancer worldwide. With an overall 5-year survival rate of 15-25%, it is the sixth leading cause of cancer-associated mortality [1]. These epidemiological data include both histological subtypes: adenocarcinoma (AC) and squamous cell carcinoma (SCC), which is the predominant type [2]. Multimodal therapy combining (neoadjuvant) chemo-/radiotherapy and resection improves the outcome in non-metastatic patients [3]. However, up to 88.9% of the patients develop metastases within 3 years after curative surgery, with a median disease-free interval after surgery of 1 year [4,5,6,7]. Due to limited therapy options, the prognosis after recurrence is extremely poor, with a median survival of 3-7 months [8,9,10]. Moreover, guidelines from the European Society for Medical Oncology (ESMO) report that palliative chemotherapy for stage IV patients is less effective for SCC than for AC. Cisplatin-based combinations tend to show an increased response rate but no benefit regarding survival; therefore, either best supportive care or monotherapy should be considered in ESCC [11]. In contrast, in various tumor entities metastases limited in number and extent (i.e. oligometastases) are increasingly considered suitable for localized therapy with possible curative intent or at least systemic control, e.g. colorectal cancer [12,13]. Such localized therapy might include surgery but also image-guided local ablation techniques like radiofrequency ablation or high-dose-rate brachytherapy (IBT). However, resection is not possible in majority of patients due to distribution of metastases, contraindications for surgery, or general anesthesia, apart from surgery-associated morbidity and mortality. IBT of parenchymal or-

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gans is a relatively new technique, where an ^{192}Iridium source is inserted directly in metastatic lesion through percutaneously implanted applicators, placed in an image-guided minimal invasive intervention, and allowing a well-defined single fraction irradiation of the target volume. IBT has already been shown to be an efficient, yet gentle treatment with a minimum of complications in ablation of metastases of various tumors, e.g. colorectal cancer or malignant melanoma, or even gastroesophageal adenocarcinoma [14,15,16]. To our knowledge, no data has been published so far evaluating the efficacy of IBT in the treatment of visceral and lung metastases of SCC. In this study, we analyzed safety and efficacy in a cohort of 11 patients with 21 unresectable SCC metastases, who underwent image-guided IBT.

Material and methods

Eligibility criteria and patients

Inclusion criteria were: 1. Technically unrespectable metastases; 2. Surgery refusal or medical contraindication for resection or comorbidities; 3. The Eastern Cooperative Oncology Group (ECOG) performance status below 2; 4. Appropriate coagulation parameters (i.e. platelet count above 50 000/nl, Quick > 50%, partial thromboplastin time > 5 seconds) and liver parameters (bilirubin < 30 µmol/l); 5. Sufficient lung capacity in case of ablation of pulmonary metastases (FEV_1 > 1.5 l). There were no limitations placed upon size or location of the lesions. Contraindications were as follows: 1. Peritoneal carcinomatosis; 2. Extensive uncontrollable systemic disease; 3. Lack of consent. With respect to these criteria, we included 11 patients in this retrospective study (all male; mean age: 64.7 years; range: 52-77) with 21 unresectable metastases, treated with computed tomography (CT)- and magnetic resonance imaging (MRI)-guided IBT between April 2009 and June 2017. We treated a total of 14 visceral metastases (including 9 liver lesions, 4 lymph node metastases, and one lesion located in the adrenal gland) and 7 lung metastases. A positive opinion from the ethics committee for the analysis of the patients' data was obtained. All patients were discussed in an interdisciplinary tumor conference, where the indication for IBT was determined. All patients were presented with histologically proven SCC and displayed tumor progression at the time of referral to our institution.

Table 1. Patients characteristics

Patient	Sex	Age (years)	M1	Chemotherapy before IBT	Localization of target lesion	Number of lesions	Max diameter (cm)	Number of caterers used per lesion	Dose appl. (Gy)	Median follow-up (months)
1	M	59	synchron	carboplatin, paclitaxel	liver	1	4.1	3	20.5	3.1
2	M	52	metachron	cisplatin, fluorouracil	lung, lymph node	2	5.8/2.6	3/2	11.3/10	3.2
3	M	77	metachron	carboplatin, paclitaxel, cisplatin, fluorouracil	liver	1	6.3	5	22.5	5.6
4	M	72	metachron	carboplatin, paclitaxel, cisplatin, fluorouracil	adrenal gland	1	3.4	3	20.1	6.9 (ongoing)
5	M	67	metachron	cisplatin, fluorouracil	lung, liver	4	1.8/0.7/ 0.7/5.8	1/1/1/5	21.9/22.8/ 25.3/14.3	7.3
6	M	52	synchron	cisplatin, fluorouracil	lung	1	2.7	2	20.9	6.3
7	M	71	metachron	NOS	lymph node	1	1.4	5	15.4	14.7
8	M	63	metachron	cisplatin, fluorouracil	liver	1	6.8	7	20.0	3.3
9	M	77	metachron	cisplatin, fluorouracil	lymph node	2	2.2/2.0	1/1	20.1/19.3	10.1
10	M	63	metachron	etoposid, cisplatin, fluorouracil	liver	5	3.4/2.7/ 1.2/0.9/1.9	2/1/1/1/2	21.2/17.1/ 22.5/ 22.7/ 17.8	4.7
11	M	59	synchron	NOS	lung	2	1.1/0.9	1/1	22.2/15.7	21.7

All patients underwent either surgery or irradiation of the primary tumor prior to local ablation.
Patient No. 1 and No. 9 received palliative chemotherapy in the time between interstitial high-dose-rate brachytherapy (HDR IBT = IBT) and progression. Furthermore, patient No. 9 was treated with RFA of the lung 3 months after IBT
IBT – interstitial brachytherapy; NOS – not otherwise specified

Prior to local ablation, ten patients received radiation of the primary tumor and 4 patients underwent surgical resection of the primary tumor. Furthermore, all patients had undergone palliative or adjuvant chemotherapy before IBT (detailed patient characteristics are presented in Table 1). Due to the size and location, two liver lesions were treated with MRI-guided IBT (maximum diameter 1.2 cm and 1 cm, respectively) and other lesions were visualized with CT. Prior to local ablation, all patients received a full clinical status evaluation with a physical examination, laboratory assessment, whole body contrast enhanced CT, and a Gb-EOB-DTPA enhanced MRI of the liver (Primovist®, Bayer, Pharma, Leverkusen, Germany). All patients undergoing IBT of lung lesions had a clinically full-compensated lung function.

Study design and statistical analysis

Primary endpoint was local tumor control; secondary endpoints were safety, overall survival, and progression-free survival. The results were analyzed in a non-randomized and retrospective approach. Local tumor control (LTC), overall survival (OS), and progression-free survival (PFS) were evaluated using the Kaplan-Meier method with SPSS (IBM Corp. released 2013; IBM SPSS Statistics for Windows, version 22.0. Armonk, NY, IBM Corp). Safety was evaluated descriptively.

Interventional technique and irradiation

The applied methodology has been described in detail elsewhere [17,18]. In short, under guidance of a fluoroscopy-CT (Toshiba, Aquilion, Japan) or real-time MRI at 1.0 T (Panorama 1.0 T, open MR system, Philips Healthcare), 18-gauge needle were placed into target lesions. Subsequently, a flexible 6F catheter sheath (Radifocus, Terumo™, Tokyo, Japan) was inserted over a stiff angiography guide wire (Amplatz, Boston Scientific, Marlborough, USA) using Seldinger's-technique, followed by the placement of a 6F afterloading catheter (Afterloadingkatheter, Primed® Medizintechnik GmbH, Halberstadt, Germany), which ends were secured to the skin with a suture and covered with sterile bandages. The described procedure was performed under a local anesthesia (lidocaine), sedation (midazolam), and analgesia (fentanyl). After catheter positioning, a contrast-enhanced CT in breath-holding technique or a gadolinium-based MRI scan were obtained to confirm correct catheter positioning and for the purpose of treatment planning. On the acquired images, the target volume was outlined precisely as gross tumor volume (GTV), the clinical target volume (CTV), and adjacent organs at risk (OAR) were marked by the interventional radiologist and the radiooncologist. Treatment planning was performed using Oncentra (Oncentra® Brachy treatment planning system, Elekta AB, Stockholm, Sweden). Automatically calculated isodose lines – relative to the CTV – were controlled and adapted slice by slice. All irradiations were applied as a single fraction irradiation using an iridium-192 source, with a nominal activity of 10 Ci. A reference dose of 15-20 Gy was intended in our patients, which was defined as the minimum dose enclosing the CTV completely (D_{100}). Higher doses inside the tumor volume were permitted and not limited. Dose limitations were taken into account independent of adjacent organs at risk, for example gastric or duodenal wall (< 15 Gy/ml). After irradiation, the catheters were removed, and the puncture tracts were sealed using gelfoam or fibrin tissue glue. Figure 1 illustrates the interventional technique and irradiation planning.

Follow-up

Clinical, laboratory, and imaging follow-up (contrast enhanced whole body CT and Gb-EOB-DTPA enhanced MRI of the liver – in case of treated hepatic metastases) was performed every three months after treatment. Lo-

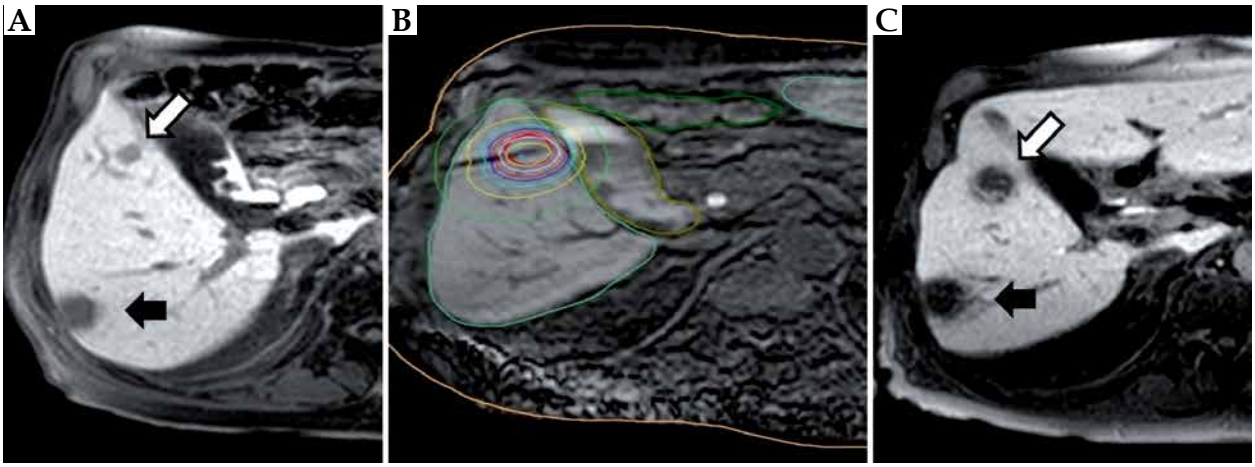

Fig. 1. A) Gd-EOB-DTPA enhanced T1w MRI of a patient with liver metastasis from esophageal squamous cell carcinoma and sequential treatment with interstitial high-dose-rate brachytherapy (HDR IBT = IBT). White arrow indicates lesion planned for IBT and black arrow shows characteristic Gd-EOB-DTPA enhancement defect after irradiation of a metastases 2 weeks before; **B)** Planning MRI with marked target lesion (red line), isodose lines, and catheters; **C)** 3 months follow-up: white arrow indicate lesion treated with Gd-EOB-DTPA enhancement defect and black arrow indicate first treated lesion with constant Gd-EOB-DTPA enhancement defect after IBT

cal tumor control and PFS were assessed by employing RECIST criteria (RECIST version 1.1). Overall survival was calculated from the day of ablation to death. Adverse events were defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Results

The median diameter of 21 metastases was 2.2 cm (range: 0.7-6.8 cm). A mean of 2.3 catheters per lesion (range: 1-7) was employed to achieve full coverage of the target lesion. Ten patients were treated in one session. One patient received 2 sessions: patient No 5 developed a solitary liver metastasis 4 months after first IBT of pulmonary and nodal lesions, and thereupon received a local treatment of the liver. The intended minimum tumor dose (D_{100}) was 15-20 Gy, depending on localization: retroperitoneal lymph node and adrenal gland were intended to treat with 15 Gy, whereas 20 Gy was prescribed for liver and lung malignancies. The median D_{100} administered was 20.1 Gy (range: 10-25 Gy). In some cases, the D_{100} had to be lowered to protect adjacent risk structures. Full dose coverage of the GTV was achieved in 5 lung lesions and 6 liver lesions (20 Gy, respectively), and a minimum of 15 Gy was reached in 4 lymph node metastases (including retroperitoneal space) as well as in the lesion of the adrenal gland. During the treatment, no adjacent OAR were irradiated in excess of critical value. The mean irradiation time was 28 min (range: 11-68 min). The mean hospital stay of the patients was 4.4 days (range: 2-7 days). None of the patients experienced grade III+ adverse events requiring interventions, surgery, or hospitalization. However, 4 patients received peri-interventional intravenous antibiosis (ciproflaxacin and metronidazole) to reduce the risk of a possible infection, e.g. due to treatment of a central liver lesion. The median follow-up time was 6.3 months (range: 3-21.8 months). Three patients displayed local recurrence of the target lesion in the timespan of 3-7 months after IBT, resulting in a local tumor control of 85.7% in the Kaplan-Meier analysis (Figure 2A). The recurrent lesions were 2 lung lesions and 1 liver metastasis; these lesions were covered with a minimum tumor dose of ≥ 20 Gy at time of treatment. The progression-free interval for all patients ranged from 1.3 to 13 months, with a median of 3.4 months (Figure 2B). During the follow-up period, all patients displayed a progressive systemic disease: 3 patients showed intrahepatic progression (27.3%), 3 patients presented pulmonary progression (27.3%), and 5 patients demonstrated progression in various locations (45.4%; i.e. lymph node, retroperitoneal space, bone). At the date of censoring, one patient of the analyzed population was still alive (Patient No. 4 received treatment in June 2017). The median OS of the 10 remaining patients after IBT was 13.7 months (range: 5.6-25.7 months, Figure 2C). Median survival after recurrence was 6 months (range: 1-22 months, Figure 2D).

Discussion

Within 3 years after curative surgery, up to 88.9% of patients with EC develop metastases, with a median disease-free interval of 1 year after resection [4,5,6,7]. The post-recurrence survival is extremely poor, with a reported median survival of approximately 3-7 months [8,19,20]. Therapy options are limited and according to the ESMO guidelines, a recommendation can be neither made for a first- nor for a second-line palliative chemotherapy in stage IV patients with SCC [11]. More recently, a phase-3, double-blind, placebo-controlled randomized trial with 450 patients failed to show a benefit of gefitinib on overall survival [20].

Whereas surgical resection is the method of choice in oligometastatic colorectal liver metastases, evidence for surgical resection of EC metastases is scarce [21,22]. Nevertheless, in metastatic EC, long-term survivors have been reported after resection of liver metastases in a curative intent [23]. Moreover, in 2017, van Daele *et al*. retrospectively analyzed the outcome of 12 stage IV patients with EC, after a multimodal and aggressive treatment including surgery [24]. Furthermore, after a median follow-up of 22 months (range: 8-50), 50% of the surgical patients were still alive. These findings suggest that highly selected candidates benefit from an aggressive curative approach, even in stage IV patients.

However, surgical resection is available in a limited number of cases (for instance in colorectal cancer), a curative resection of liver metastases is not possible in approximately 80% of the cases [21] but if possible, it is also linked to surgery-associated morbidity and mortality, regarding the extent of resection and the remaining functioning liver tissue. It results in prolonged stay in the hospital, for instance in the study mentioned above, the median post-operative hospital stay was 15 days (range: 11-52 days).

In contrast, image-guided IBT provides a safe and minimal invasive approach. In the literature for patients undergoing local ablation of liver lesions or metastases of the retroperitoneal space, grade III-IV adverse events (i.e. bleeding, requiring angiographic embolization) occurred in up to 3%, grade I and II toxicities (e.g. nausea, emesis, unspecified abdominal pain) were reported in up to 29% [18,25]. In the study herein, we did not report any severe adverse event (grade III+) requiring invasive intervention. The mean hospital stay was 4.4 days. In general, patients tolerated the treatment well and could be discharged earlier, but due to the risk of occult bleeding, an observation of at least 48 hours after ablation was considered necessary.

To our knowledge, there is a limited number of studies investigating the efficacy and outcome of patients with metastatic EC treated with local ablation. Matsui et al. retrospectively evaluated LTC of 21 patients, with a total of 31 pulmonary metastases (mean size, 1.7 cm) treated with percutaneous radiofrequency ablation (RFA) [26]. The authors reported LTC rate of 74.2% after a median interval of 4.8 months post-RFA. Baba *et al*. showed a better LTC of 83% at 12 months after RFA of pulmonary SCC metastases [27].

In contrast, IBT has primarily been evaluated in metastatic colorectal cancer and in hepatocellular carcinoma (HCC), demonstrating LTC rates of 88.3% after 12 months

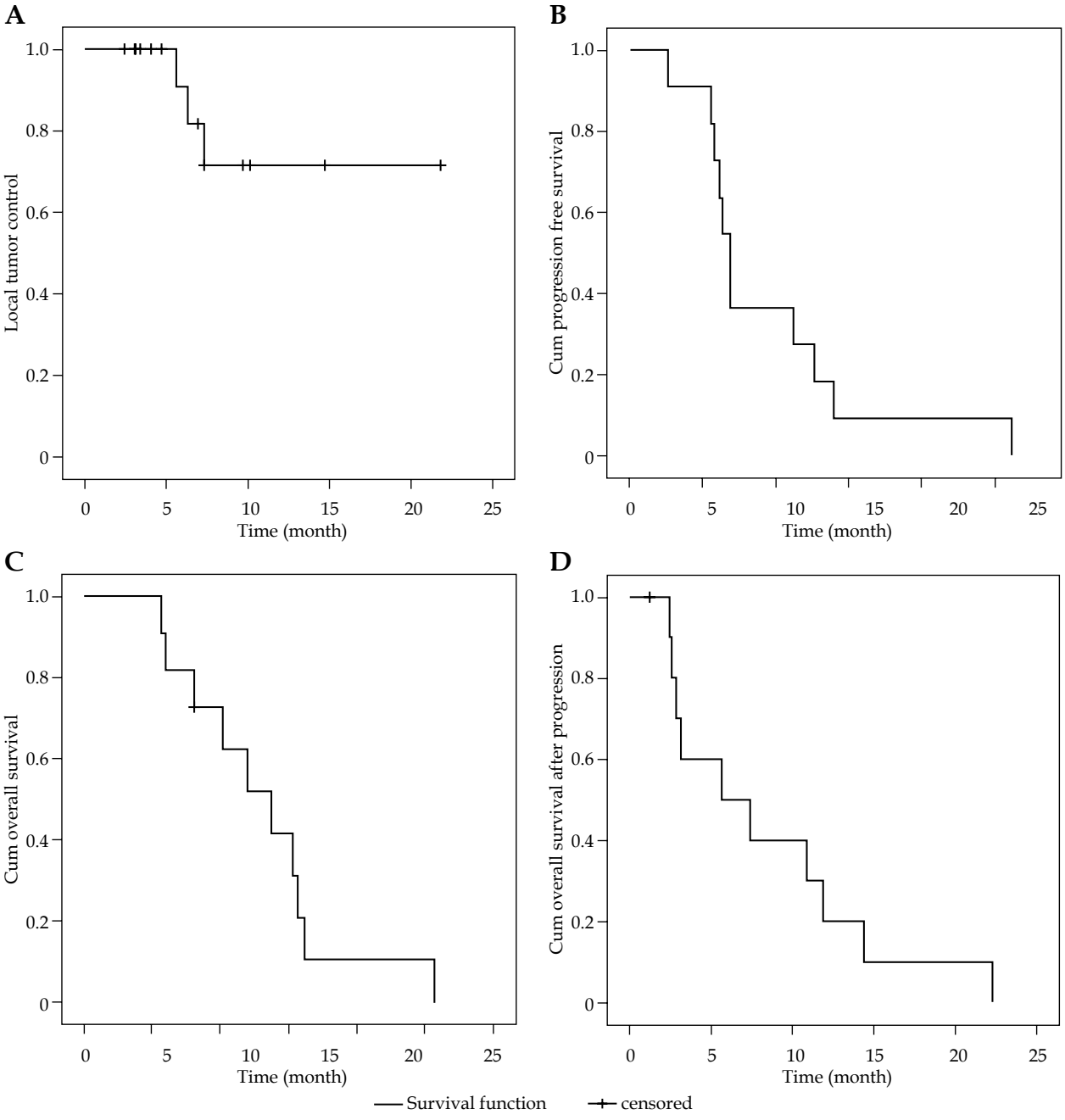

Fig. 2. Kaplan-Meier curves show **A)** local tumor control and **B)** progression-free survival of patients with squamous cell carcinoma metastases ablated with interstitial high-dose-rate brachytherapy. Overall survival and overall survival after tumor progression of the same patients is depicted in **C)**, and **D)** Censoring is indicated by crosses

for colorectal lesions and up to 95% for HCC [15,17,28]. Moreover, in metastatic malignant melanoma, the LTC rate was reported to be 90% after a median follow-up period of 5 months [14]. Furthermore, for metastases of gastric or esophageal adenocarcinoma, Geisel et al. showed LTC rate of 100% over a median follow-up of 6.1 months post IBT [16]. In our study, we report a local tumor control of 85.7% after a median follow-up of 6.3 months. The reported difference might be due to very small patients' population and relatively short follow-up period. Therefore, it can be assumed that our findings go in line with the existing literature. Moreover, our findings correspond to the results of RFA studies mentioned above, even providing a better LTC compared to the investigation of Matsui et al. However, RFA has well known technical limitations leading to a possible incomplete ablation, including a large tumor mass (maximal tumor diameter of 5 cm) and major vessels close to the target volume inducing a potential cooling effect. Additionally, adverse events can occur due to the vicinity to critical heat sensitive organs (e.g. bile duct, ureter, liver hilum). IBT in contrast is independent of these restrictions.

To our knowledge, there are only a few studies investigating the use of stereotactic body radiation therapy (SBRT) in the treatment of visceral or pulmonary metastases of EC: two case reports combining SBRT and palliative chemotherapy [29,30], and two studies investigating the effect of SBRT in oligometastatic disease and in solitary/limited number of nodal metastases, both studies including lesions of any primary site, i.e. 2 and 1 patients with EC, respectively [31,32].

A widespread systemic progression is known to be the major limiting factor for survival, concluding that our finding of a median PFS of 3.4 months emphasizes the poor overall survival of patients with metastasized EC. Consistently, Geisel *et al*. reported a median PFS of 3.5 months in patients with metastatic esophageal adenocarcinoma after IBT [16].

In our study, we report a median overall survival of 13.7 months after IBT, with a range of 5.6-25.7 months. These findings underline that the impact of local ablation on overall survival is not yet clarified, especially considering the fact that in metastasized SCC, chemotherapeutic options are missing. After recurrence, the survival was poor with a median of 6 months corresponding to the findings in the literature [8]. Nevertheless, we also report one long-term survivor with 25 months. After an aggressive multimodal approach including surgery, van Daele *et al*. reported a median OS of 22 months indicating possible long-term survival of selected stage IV patients [24]. To identify appropriate candidates that might benefit from local ablation with the intent to extend survival, a prospective trial is needed.

Therefore, the limitations of the study include its retrospective nature and the low number of patients as well as relatively short follow-up. However, to our knowledge, there is little data regarding local ablation of metastatic EC and despite its limitations, the results of this study demonstrate that IBT can be safely and effectively used in the local control of metastasized SCC. Moreover, together with the findings of van Daele *et al*., this investigation provides an indication that a more aggressive approach could improve the overall survival of highly selected stage IV patients, with an emphasis on the advantage that IBT is a well-tolerated procedure with few side effects.

Conclusions

We conclude that high-dose-rate brachytherapy is a safe and well-tolerated treatment in the local tumor control of patients with metastasized squamous cell carcinoma.

Disclosure

Authors report no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136: 359-386.
2. Jain S, Dhingra S. Pathology of esophageal cancer and Barrett's esophagus. *Ann Cardiothorac Surg* 2017; 6: 99-109.
3. Van Rossum PSN, Mohammad NH, Vleggaar FP et al. Treatment for unresectable or metastatic oesophageal cancer: current evidence and trends. *Nat Rev Gastroenterol Hepatol* 2018; 15: 235-249.
4. Nakagawa S, Kanda T, Kosugi S et al. Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. *J Am Coll Surg* 2004; 198: 205-211.
5. Mariette C, Balon JM, Piessen G et al. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. *Cancer* 2003; 97: 1616-1623.
6. Hulscher JB, van Sandick JW, Tijssen JG et al. The recurrence pattern of esophageal carcinoma after transhiatal resection. *J Am Coll Surg* 2000; 191: 143-148.
7. Kunisaki C, Makino H, Takagawa R et al. Surgical outcomes in esophageal cancer patients with tumor recurrence after curative esophagectomy. *J Gastrointest Surg* 2008; 12: 802-810.
8. Abate E, DeMeester SR, Zehetner J et al. Recurrence after esophagectomy for adenocarcinoma: defining optimal follow-up intervals and testing. *J Am Coll Surg* 2010; 210: 428-435.
9. Dresner SM, Griffin SM. Pattern of recurrence following radical oesophagectomy with two-field lymphadenectomy. *Br J Surg* 2000; 87: 1426-1433.
10. Blom RL, Lagarde SM, van Oudenaarde K et al. Survival after recurrent esophageal carcinoma has not improved over the past 18 years. *Ann Surg Oncol* 2013; 20: 2693-2698.
11. Lordick F, Mariette C, Haustermans K et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; 27: v50-v57.
12. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol* 2011; 8: 378-382.
13. Aigner F, Pratschke J, Schmelzle M. Oligometastatic disease in colorectal cancer – how to proceed. *Visc Med* 2017; 33: 23-28.
14. Bretschneider T, Mohnike K, Hass P et al. Efficacy and safety of image-guided interstitial single fraction high-dose-rate brachytherapy in the management of metastatic malignant melanoma. *J Contemp Brachytherapy* 2015; 7: 154-160.
15. Collettini F, Lutter A, Schnapauff D et al. Unresectable colorectal liver metastases: percutaneous ablation using CT-guided high-dose-rate brachytherapy (CT-HDBRT). *Rofo* 2014; 186: 606-612.
16. Geisel D, Denecke T, Collettini F et al. Treatment of hepatic metastases from gastric or gastroesophageal adenocarcinoma with computed tomography-guided high-dose-rate brachytherapy (CT-HDRBT). *Anticancer Res* 2012; 32: 5453-5458.
17. Ricke J, Wust P, Stohlmann A et al. CT-guided interstitial brachytherapy of liver malignancies alone or in combination with thermal ablation: phase I-II results of a novel technique. *Int J Radiat Oncol Biol Phys* 2004; 58: 1496-1505.
18. Bretschneider T, Ricke J, Gebauer B, Streitparth F. Image-guided high-dose-rate brachytherapy of malignancies in various inner organs - technique, indications, and perspectives. *J Contemp Brachytherapy* 2016; 8: 251-261.
19. Parry K, Visser E, van Rossum PS et al. Prognosis and treatment after diagnosis of recurrent esophageal carcinoma following esophagectomy with curative intent. *Ann Surg Oncol* 2015; 22 (Suppl 3): S1292-1300.
20. Dutton SJ, Ferry DR, Blazeby JM et al. Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. *Lancet Oncol* 2014; 15: 894-904.
21. Garden OJ, Rees M, Poston GJ et al. Guidelines for resection of colorectal cancer liver metastases. *Gut* 2006; 55: iii1-iii8.
22. Nguyen KT, Laurent A, Dagher I et al. Minimally invasive liver resection for metastatic colorectal cancer: a multi-insti-

tutional, international report of safety, feasibility, and early outcomes. *Ann Surg* 2009; 250: 842-848.
23. Huddy JR, Thomas RL, Worthington TR, Karanjia ND. Liver metastases from esophageal carcinoma: is there a role for surgical resection? *Dis Esophagus* 2015; 28: 483-487.
24. Van Daele E, Scuderi V, Pape E et al. Long-term survival after multimodality therapy including surgery for metastatic esophageal cancer. *Acta Chir Belg* 2018; 118: 227-232.
25. Mohnike K, Neumann K, Hass P et al. Radioablation of adrenal gland malignomas with interstitial high-dose-rate brachytherapy: Efficacy and outcome. *Strahlenther Onkol* 2017; 193: 612-619.
26. Matsui Y, Hiraki T, Gobara H et al. Percutaneous radiofrequency ablation for pulmonary metastases from esophageal cancer: retrospective evaluation of 21 patients. *J Vasc Interv Radiol* 2014; 25: 1566-1572.
27. Baba Y, Watanabe M, Kawanaka K et al. Radiofrequency ablation for pulmonary metastases from esophageal squamous cell carcinoma. *Dis Esophagus* 2014; 27: 36-41.
28. Mohnike K, Wieners G, Schwartz F et al. Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: safety, efficacy, and effect on survival. *Int J Radiat Oncol Biol Phys* 2010; 78: 172-179.
29. Katano A, Yamashita H, Nakagawa K. Stereotactic body radiotherapy for oligo-recurrence in the liver in a patient with esophageal carcinoma: A case report. *Mol Clin Oncol* 2017; 7: 1061-1063.
30. Egawa T, Okubo Y, Kemmochi T et al. A case of liver metastasis from esophageal cancer treated with stereotactic body radiation therapy. *Gan To Kagaku Ryoho* 2013; 40: 1850-1852.
31. Milano MT, Katz AW, Zhang H et al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys* 2012; 83: 878-886.
32. Yeung R, Hamm J, Liu M, Schellenberg D. Institutional analysis of stereotactic body radiotherapy (SBRT) for oligometastatic lymph node metastases. *Radiat Oncol* 2017; 12: 105.

Veröffentlichung 15

Radioablation by Image-Guided (HDR) Brachytherapy and Transarterial Chemoembolization in Hepatocellular Carcinoma: A Randomized Phase II Trial.

Mohnike K, Steffen IG, Seidensticker M, Hass P, **Damm R**, Peters N, Seidensticker R, Schütte K, Arend J, Bornschein J, Streitparth T, Wybranski C, Wieners G, Stübs P, Malfertheiner P, Pech M, Ricke J.

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Radioablation by Image-Guided (HDR) Brachytherapy and Transarterial Chemoembolization in Hepatocellular Carcinoma: A Randomized Phase II Trial

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Abstract

Background and Aims The aim of this single-center, open-label phase II study was to assess the efficacy of image-guided high-dose-rate (HDR) brachytherapy (iBT) compared with conventional transarterial embolization (cTACE) in unresectable hepatocellular carcinoma.

Methods Seventy-seven patients were treated after randomization to iBT or cTACE, as single or repeated interventions. Crossover was allowed if clinically indicated. The primary endpoint was time to untreatable progression (TTUP). Eligibility criteria included a Child–Pugh score of ≤ 8 points, absence of portal vein thrombosis (PVT) at the affected liver lobe, and ≤ 4 lesions. Survival was analyzed by using the Cox proportional hazard model with stratification for Barcelona Clinic Liver Cancer (BCLC) stages.

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Results Twenty patients were classified as BCLC-A (iBT/cTACE 8/12), 35 as BCLC-B (16/19), and 22 as BCLC-C (13/9). The 1-, 2-, and 3-year TTUP probabilities for iBT compared with cTACE were 67.5% versus 55.2%, 56.0% versus 27.4%, and 29.5% versus 11.0%, respectively, with an adjusted hazard ratio (HR) of 0.49 (95% confidence interval 0.27–0.89; $p = 0.019$). The 1-, 2-, and 3-year TTPs for iBT versus cTACE were 56.0% versus 28.2%, 23.9% versus 6.3%, and 15.9% versus 6.3%, respectively, with an adjusted HR of 0.49 (0.29–0.85; $p = 0.011$). The 1-, 2-, and 3-year OS rates were 78.4% versus 67.7%, 62.0% versus 47.3%, and 36.7% versus 27.0%, respectively, with an adjusted HR of 0.62 (0.33–1.16; $p = 0.136$).
Conclusions This explorative phase II trial showed a superior outcome of iBT compared with cTACE in hepatocellular carcinoma and supports proceeding to a phase III trial.

Keywords Ablation · Liver cancer · BCLC · HCC · RCT

Abbreviations

AASL	American Association for the Study of the Liver
BCLC	Barcelona Clinic Liver Cancer (staging system)
CI	Confidence interval
CLIP	Cancer of the Liver Italian Program
CT	Computed tomography
cTACE	Conventional transarterial chemoembolization
CTCAE	Common Terminology Criteria for Adverse Events
DEB-TACE	Drug-eluting beads transarterial chemoembolization
EASL	European Association for the Study of the Liver
HCC	Hepatocellular carcinoma
HDR	High dose rate
HR	Hazard ratio
iBT	Interstitial brachytherapy
OS	Overall survival
PVT	Portal vein thrombosis
RFA	Radiofrequency ablation
SBRT	Stereotactic body radiotherapy
TTP	Time to progression
TTUP	Time to untreatable progression

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Introduction

In Europe, five-year survival rates of up to 51% have been shown for hepatocellular carcinoma (HCC) suitable for resection [1]. Unfortunately, 70–80% of patients are not candidates for resection, because of advanced cirrhosis, multiple lesions or diffuse tumor growth, and comorbidity. Liver transplantation is the only potentially curative option at present, with five-year post-transplantation survival rates of up to 70% for patients in early stages of disease [2]. The treatment of choice in the intermediate stage is transarterial chemoembolization ('conventional TACE' = cTACE; 'drug-eluting beads TACE' = DEB-TACE). In clinical practice, TACE is also applied in BCLC (Barcelona Clinic Liver Cancer stage)-A patients, often as an adjunct to radiofrequency ablation (RFA), and in BCLC-C patients, for whom sorafenib-only treatment is not considered appropriate [3–6]. However, effectiveness and feasibility of TACE are limited by factors such as advanced-stage cirrhosis, a hampered general condition and portal vein invasion. In ipsilateral complete portal vein thrombosis (PVT), TACE is known to be associated with a risk of ischemia and abscess formation. Thermal ablation is usually considered up to a tumor size of 3 cm. Beyond this limit, local recurrence rates increase [7, 8]. Some authors state the superiority of Gelaspon particles over Lipiodol for embolization purposes [9]. A recently invented method, CT (computed tomography)-guided interstitial HDR (high-dose-rate) brachytherapy (iBT), has successfully been used in various neoplasms of the liver and other sites [10–18]. As a unique feature, iBT is not restricted by tumor size or heat sink effect and PVT is not a contraindication [19–22].

A recent study encouraged us to address the clinical value of iBT as compared with standard treatment such as TACE in a future trial. A major intention of this explorative type II study was to investigate whether proceeding to phase III trial is supported [11].

Patients and Methods

Patient Population and Eligibility Criteria

Patient recruitment took place from October 2006 to September 2010. Patients with a diagnosis of HCC were randomized to receive either CT-guided HDR iBT or cTACE. Inclusion criteria were:

- Diagnosis of HCC by histopathology or according to the criteria of the Consensus Conference of the European Association for the Study of Liver Disease
- Unresectable HCC
- Karnofsky Index > 70
- Estimated life expectancy > 16 weeks
- Adequate bone marrow function
- Adequate contraception for female patients
- Informed consent

Exclusion criteria were as follows:

- PVT on the tumor side
- Extrahepatic spread
- Child C
- Other untreated malignant diseases
- General contraindication for chemotherapy
- Active infectious disease
- Neuropathy, platin-allergy
- Pregnancy

All patients were rated unresectable and not eligible for radiofrequency ablation owing to lesion size and/or location.

All patients received a full clinical status evaluation at inclusion, comprising a physical examination, extensive laboratory assessments, whole-body computed tomography, and MRI of the liver (Fig. 1).

Study Design

The study represents an exploratory randomized phase II approach comparing two interventional treatment arms. The study was registered at clinicaltrials.gov (NCT00807300), and the study protocol conformed with the Declaration of Helsinki. The institutional review board approved the study, and informed consent was obtained from all patients. This explorative phase II study analyzes the efficacy and safety of iBT in comparison with cTACE and aims to generate a hypothesis for a potential phase III study. A high type I error of 20% was allowed to keep patient numbers reasonable, and the sample size was set to 80 including a dropout rate of 10% [23]. Owing to slower patient accrual the trial was closed with a lower patient number than anticipated. However, the minimum target sample size (without dropouts) was achieved.

Patients meeting the inclusion criteria were randomly assigned to first treatment either with cTACE (control arm) or with iBT (experimental arm). Simple randomization was performed allocating patients sequentially to treatment groups using shuffled sealed opaque envelopes containing equal numbers of identifiers for treatment A and treatment B. After untreatable progression had been reached, any further treatment decisions were left to the investigator's judgment.

The primary endpoint was the time to untreatable progression (TTUP), defined as the time from the first treatment (either iBT or cTACE) to the time point when complete tumor ablation could not be repeated any further by applying the assigned method. The criteria for stopping the assigned treatment were as follows:

- No radiological response at follow-up/local failure
- Diffuse progression (> 3 new lesions)
- Chronic hepatic decompensation, as defined by a Child–Pugh score deterioration of $\geq$ 2 points
- Clinical conditions other than hepatic decompensation, permanently precluding further treatment (e.g., performance status).

Technique-associated no-go criteria possibly occurring during follow-up, such as failure of Lipiodol to accumulate in the lesion, missing angiographic visibility, development of ipsilateral PVT, development of an arterioportal shunt visible by angiography (all cTACE), or contraindications to a percutaneous interstitial approach (only iBT, including severe coagulopathy and uncontrolled ascites), were not counted, in order to ensure that the criteria for TTUP were the same in the two groups. The corresponding time points were censored.

Secondary endpoints were time to progression (TTP) and overall survival (OS).

Interstitial HDR Brachytherapy (iBT)

The technique of CT-guided brachytherapy has been described in detail elsewhere [18, 19]. We performed irradiation employing the HDR brachytherapy technique based on a 10-Ci Iridium-192 source. Positioning of the brachytherapy catheters was performed by fluoroscopy CT. For analgosedation, fentanyl and midazolam were used according to individual requirement.

The target dose was defined as the minimum dose taken up by the visible tumor margin. We prescribed a minimum target dose of 15 Gy, based on the results of two pilot studies [20, 21].

Transarterial Chemoembolization (cTACE)

After puncture of the right or left femoral artery, an angiography of the celiac artery and superior mesenteric artery via a 4F catheter was performed. Parasitic feeders to HCC lesions were searched for with the same catheter. Chemoembolization was conducted in a supraselective manner with a 3F microcatheter, applying the drug/oil emulsion over the feeding arteries of the tumor only. Typically, 30–50 mg/m^2 doxorubicin and cisplatin mixed

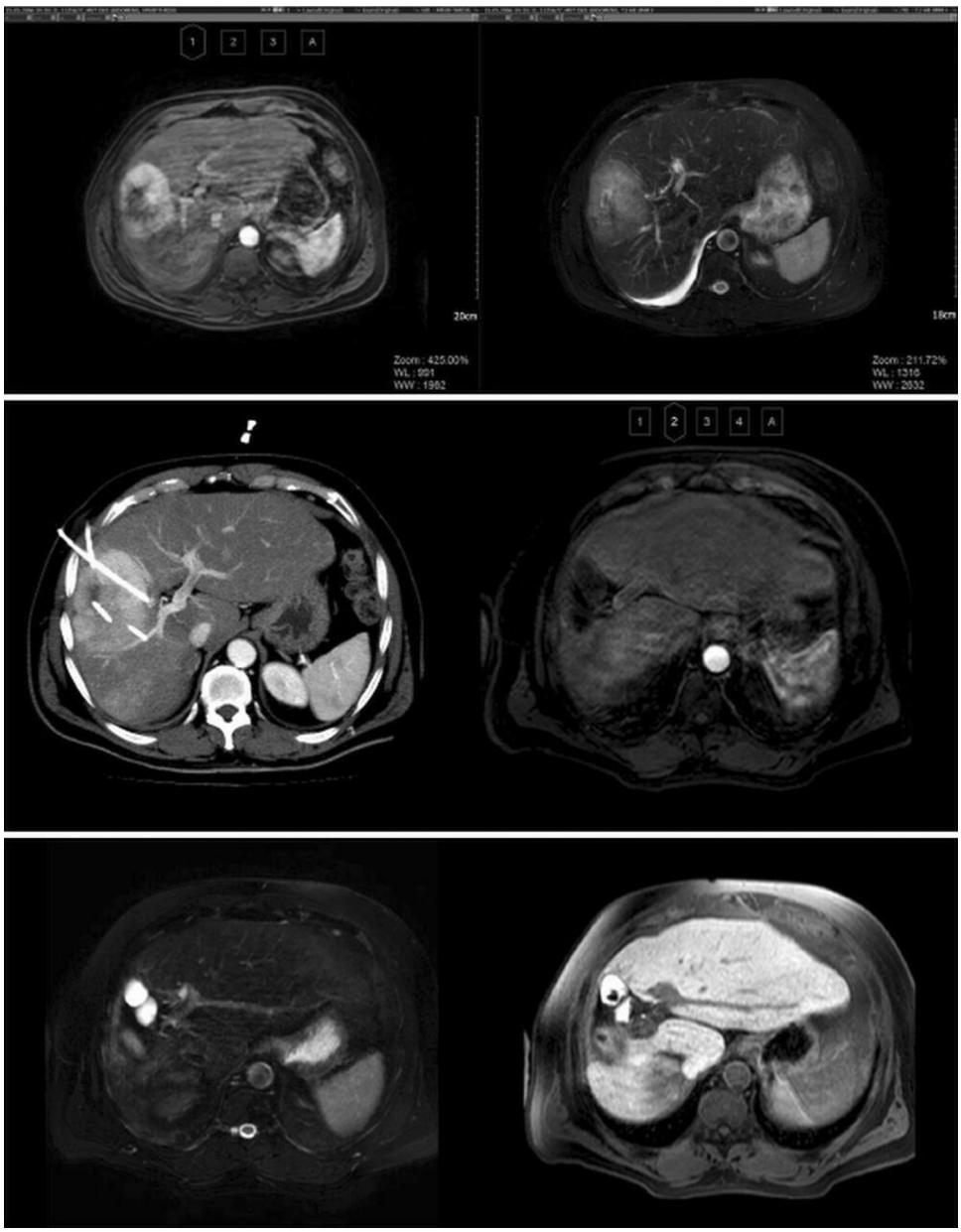

Fig. 1 Complete remission of a single hepatocellular carcinoma (8.3 cm) of the right liver lobe. The patient refused surgery. Upper row: before treatment, arterial phase (left) and T2 FS (right), May 2006. Middle row: Left: catheter placement during treatment. Right: arterial phase, June 2014. Bottom row: left: T2 FS. Right: T1 WATS late contrast phase (GD-EOB-DTPA). Note the completely ablated segment with prolapsed intestinal loops

with Lipiodol were administered. If the total tumor volume or tumor count could not be embolized in one session, the procedure was repeated after 6 weeks.

Assessments

Before therapy a physical examination, MRI and computed tomography (CT) scans, and laboratory tests were performed. These examinations were repeated every 3 months. Clinical evaluators (two experienced radiologists, consensus decision) were blinded to the chosen treatment.

Since the mRECIST criteria for tumor response had not been established for HCC in 2006, TTP was likewise assessed by following the recommendations of the European Association for the Study of the Liver (EASL) and American Association for the Study of the Liver (AASL) [24, 25].

Patients were censored at the time point of liver transplantation, liver resection, or crossover treatment. After untreatable progression (the primary endpoint TTUP) had been reached, any further treatment decisions were left to the investigator's judgment.

Statistical Methods

The program suite IBM SPSS Statistics 22.0 and R version 3.1.3 (The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis.

Metric parameters are described using median and interquartile range (25th–75th percentile), and the Mann–Whitney U test was used for analyzing differences between unpaired groups. Categorical variables were analyzed by using contingency tables, the Chi-square test and Fisher's exact test.

The observation period was 5 years. Patients were censored at crossover treatment, at loss to follow-up, and at the end of observation period. TTUP, TTP, and OS were estimated by the Kaplan–Meier (KM) method, and the Cox proportional hazard model was used to assess the association of TTUP, TTP, and OS with covariates. Parameters with p value ≤ 0.1 in univariate Cox regression were included in a multivariate Cox proportional hazard analysis. The multivariate model was optimized by using the Akaike information criterion with stepwise backward elimination. Analysis was performed on an intention-to-treat (ITT) basis (TTP, TTUP, and OS) and 'as treated' (safety). The Cox proportional hazard model was stratified for BCLC stages, as this parameter did not satisfy the proportional hazard assumption, which was assessed visually from log–log KM curves. Significance was assumed at a p value less than 0.05.

Results

Patients

In total, 392 patients were assessed for eligibility from October 2006 to September 2010. Of these patients 203 did not meet the inclusion criteria, 68 declined to participate, and 44 were excluded for other reasons. Of the remaining 77 patients 40 were randomly assigned to the cTACE group and 37 patients to the iBT group. Two patients allocated to receive cTACE were transferred to the iBT group for technical reasons. Thus, the per-protocol population comprised 38 patients in the cTACE group and 39 patients in the iBT group (Fig. 2).

Among the 77 enrolled patients (13 females and 64 males; mean age 68.5 years; range 43.4–82.7 years), in 34 patients, HCC was confirmed by biopsy (44%), whereas in 43 patients with cirrhosis, HCC was diagnosed on the basis of noninvasive criteria according to the EASL and AASL guidelines [24, 25]. Patient characteristics are summarized in Table 1.

Treatments and Follow-up

The number of treatments per patient was significantly lower in the iBT group (2.5 ± 1.6) compared with the cTACE group (4.0 ± 3.2, $p = 0.039$). Subsequent treatments after the end-of-study date are shown in Table 2.

In 8 of the 38 patients in the cTACE group, treatment had to be stopped for technique-related reasons such as AV shunts or ipsilateral PVT. Owing to missing visibility in CT or MRI, treatment had to be stopped in a patient with AFP recurrence in the iBT group. The difference was statistically significant (Chi-square test, $p = 0.012$).

During the 5-year observation period 52 patients died (iBT, $n = 31$; cTACE, $n = 21$) and 15 patients were censored because of crossover treatment after reaching

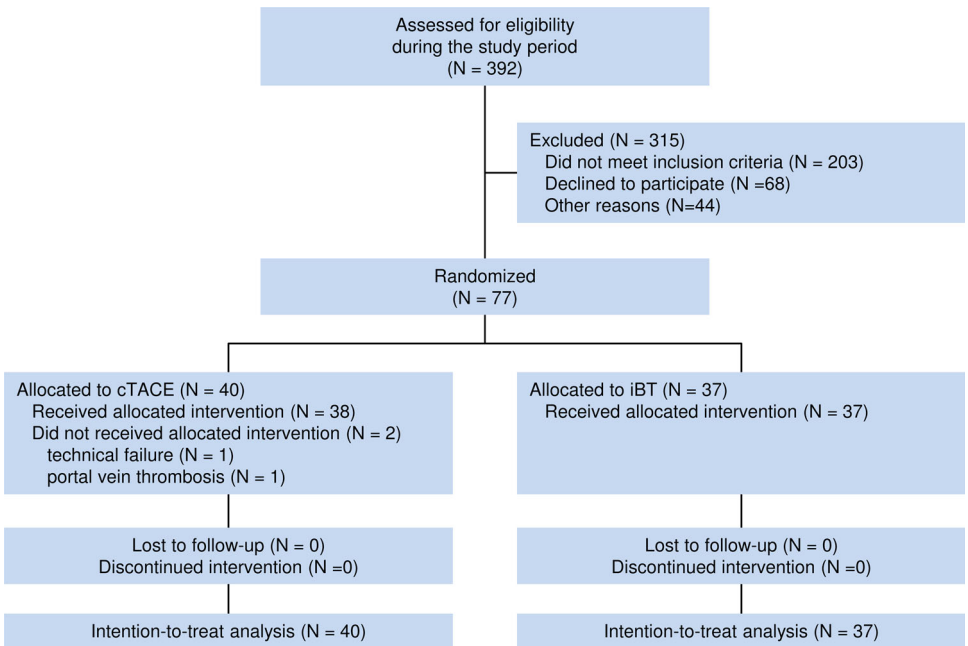

Fig. 2 CONSORT diagram for the trial

Table 1 Baseline patient characteristics

Characteristic	iBT (n = 37)	cTACE (n = 40)	p
Age at study inclusion (years), mean ± SD	69.3 ± 7.4	67.7 ± 9.0	0.419
Sex			0.881
Male	31 (84%)	33 (83%)	
Female	6 (16%)	7 (17%)	
Pretreatment AFP (ng/ml), median (IQR)	13 (4–258)	12 (5–83)	0.842
Pretreatment bilirubin (μmol/l), median (IQR)	12.2 (9.9–15.7)	18.9 (11.4–28.9)	**0.007**
Number of lesions, median (IQR)	2 (1–3)	2 (1–3)	0.466
Longest diameter (cm), median (IQR)	4.5 (3.0–6.5)	3.6 (2.1–6.6)	0.359
BCLC stage			0.434
A	8 (22%)	12 (30%)	
B	16 (43%)	19 (48%)	
C	13 (35%)	9 (22%)	
Child–Pugh class			0.194
A	36 (97%)	36 (90%)	
B	1 (3%)	4 (10%)	
Cirrhosis			0.388
Yes	32 (87%)	37 (93%)	
No	5 (13%)	3 (7%)	
HCC diagnosis			0.539
Biopsy	15 (40%)	19 (47%)	
Noninvasive	22 (60%)	21 (53%)	
Etiology			0.416
Alcohol abuse	13 (35%)	17 (42.5%)	
Nonalcoholic steatohepatitis	10 (27%)	7 (17.5%)	
Hepatitis C	7 (19%)	6 (15%)	
Hepatitis C + alcohol abuse	0	1 (2.5%)	
Hepatitis B	2 (5.5%)	0	
Hemochromatosis	0	2 (5%)	
Primary biliary cirrhosis	0	1 (2.5%)	
Cryptogenic	5 (13.5%)	6 (15%)	
Pretreatments			0.725
Untreated	31 (83.8%)	35 (87.5%)	
Resection	1 (2.7%)	2 (5%)	
Resection + sorafenib	1 (2.7%)	0	
Radiofrequency ablation	1 (2.7%)	1 (2.5%)	
Percutaneous ethanol installation	1 (2.7%)	0	
Sorafenib	1 (2.7%)	1 (2.5%)	
Resect. + percutaneous ethanol installation	1 (2.7%)	0	
Systemic therapy other than sorafenib	0	1 (2.5%)	

Bold value indicates $p < 0.05$

untreatable progression (14 patients of the cTACE arm received iBT and 1 patient in the iBT arm received cTACE) at a mean follow-up time of 15.5 months (SD 9.3 months; range 3.1–38.5 months). Of the remaining 10 patients 6 were still alive at the end of the 5-year observation period and the mean follow-up time was 41.2 months (SD 24.6 months; range 4.9–60 months).

Survival

The 1-, 2-, and 3 year TTUP survival rates for the iBT compared with the cTACE group were 67.5% versus 55.2%, 56.0% versus 27.4%, and 29.5% versus 11.0%, respectively, with an HR of 0.52 (0.30–0.90; p = 0.021; Fig. 3A). Stratifying by BCLC stages revealed an HR of 0.92 (95% CI 0.31–2.72; p = 0.887) for BCLC-A, 0.38 (95% CI 0.16–0.87; p = 0.021) for BCLC-B, and 0.51

Table 2 Treatment characteristics

	iBT (n = 37)	**cTACE** (n = 40)	p
Number of treatments before untreatable progression, mean ± SD	2.5 ± 1.6	4.0 ± 3.2	**0.039**
TTUP: dominant terminating events			
Diffuse progression	18 (48.6%)	13 (32.5%)	0.953
Hepatic decompensation	3 (8.1%)	4 (10.0%)	0.544
Performance status	3 (8.1%)	3 (7.5%)	0.699
Local failure	0	2 (5.0%)	0.267
Death	7 (18.9%)	6 (15%)	0.777
Subsequent therapies			
Liver transplantation	1 (2.7%)	4 (10%)	0.204
Resection	0	1 (2.5%)	0.519
Radiofrequency ablation (RFA)	1 (2.7%)	1 (2.5%)	0.772
Radioembolization	4 (10.8%)	5 (12.5%)	0.551
Systemic therapy with sorafenib	13 (35.1%)	13 (32.5%)	0.686
Crossover treatment	1 (2.7%)	14 (35%)	**< 0.001**

Bold values indicate $p < 0.05$

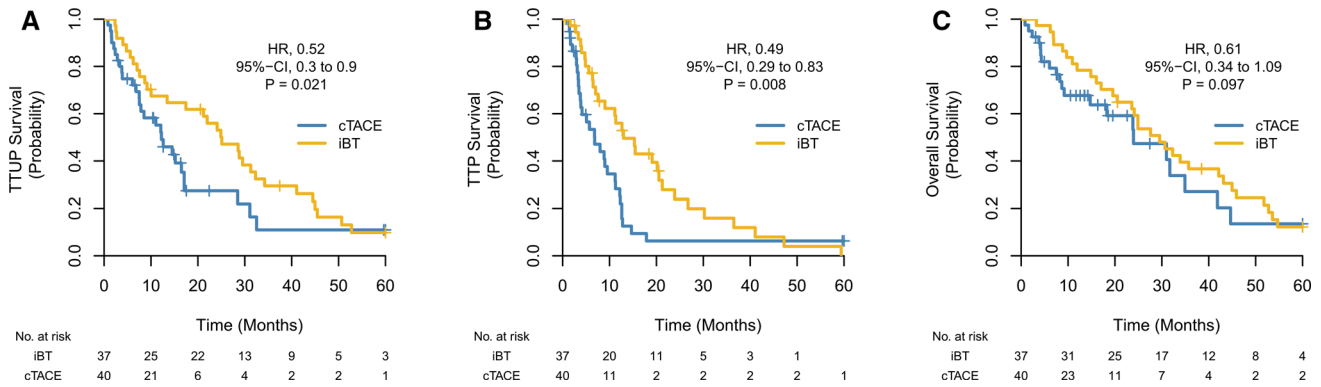

Fig. 3 Kaplan–Meier curves depicting time to untreatable progression (**A**), time to progression (**B**), and overall survival (**C**)

(95% CI 0.18–1.42; $p = 0.195$) for BCLC-C (Fig. 4). Further significant influencing factors were female gender (HR = 3.31; $p = 0.001$), AFP (unit: µg/ml; HR = 1.08; $p = 0.038$), Child–Pugh score B (HR = 3.91; $p = 0.018$), and pretherapeutic bilirubin > 19 µmol/l (HR = 2.03; $p = 0.024$). Near-significance was observed for lesion diameter > 5 cm (HR = 1.82; $p = 0.057$) and the number of lesions > 2 (HR = 1.77; $p = 0.056$). The multivariate Cox regression model included female gender (HR = 4.21, $p < 0.001$), iBT arm (HR = 0.49, $p = 0.019$), the number of lesions > 2 (HR = 1.80, $p = 0.069$), AFP (unit:µg/ml; HR = 1.13, $p = 0.001$), and Child–Pugh score B (HR = 3.81; $p = 0.036$).

The 1-, 2-, and 3-year TTP survival rates for iBT compared with cTACE were 56.0% versus 28.2%, 23.9% versus 6.3%, and 15.9% versus 6.3%, respectively, with a univariate HR of 0.49 (0.29–0.83; $p = 0.008$; Fig. 3B). Stratifying by BCLC stage revealed an HR of 0.68 (95% CI 0.26–1.77; $p = 0.430$) for BCLC-A, 0.46 (95% CI 0.21–1.00; $p = 0.051$) for BCLC-B, and 0.36 (95% CI 0.13–1.06; $p = 0.063$) for BCLC-C (Fig. 4). Further significant factors in univariate Cox regression were Child–Pugh score (HR = 3.33; $p = 0.031$) and pretherapeutic bilirubin > 19 µmol/l (HR = 1.86; $p = 0.042$). Near-significance was observed for age (unit: 10 years; HR = 0.74; $p = 0.070$), the number of lesions > 2 (HR = 1.73; $p = 0.060$), and AFP (unit: µg/mol; HR = 1.08; $p = 0.058$). The multivariate Cox regression model included age (unit: 10 years; HR = 0.78; $p = 0.130$), iBT (HR = 0.49, $p = 0.011$), AFP (unit: µg/mol; HR = 1.08; $p = 0.063$), and Child–Pugh score (HR = 3.12; $p = 0.045$).

The 1-, 2-, and 3-year overall survival rates in the iBT compared with the TACE group were 78.4% versus 67.7%, 62.0% versus 47.3%, and 36.7% versus 27.0%, respectively, with a univariate HR of 0.61 (0.34–1.09; $p = 0.097$; Fig. 3C). Stratifying by BCLC stage revealed an HR of

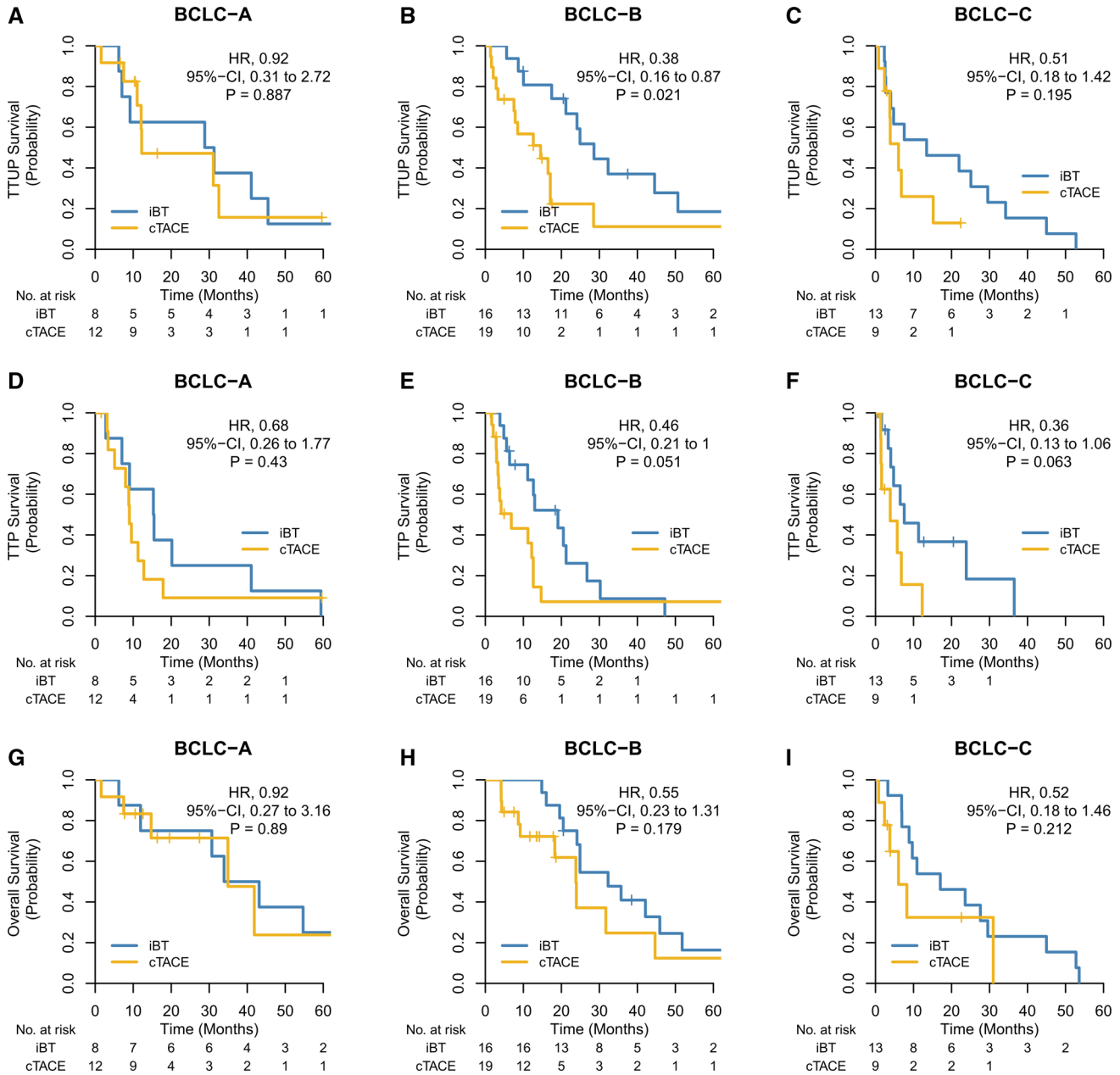

Fig. 4 Kaplan–Meier curves of time to untreatable progression (upper row), time to progression (middle row), and overall survival (lower row) stratified by BCLC (**A** left-hand column; **B** middle column; **C** right-hand column)

0.92 (95% CI 0.27–3.16; $p = 0.890$) for BCLC-A, 0.55 (95% CI 0.23–1.31; $p = 0.179$) for BCLC-B, and 0.52 (95% CI 0.18–1.46; $p = 0.212$) for BCLC-C. The univariate Cox regression model revealed female gender (HR = 2.88, $p = 0.006$), AFP (unit: µg/mol; HR = 1.12; p = 0.004), Child–Pugh score (HR = 6.19; $p = 0.002$), and pretherapeutic bilirubin > 19 µmol/l (HR = 3.33; $p < 0.001$) as significant factors and the number of lesions > 2 (HR = 1.68; $p = 0.089$) as a factor showing close significance. The multivariate Cox regression model for OS comprised female gender (HR = 3.46, $p = 0.002$), iBT (HR = 0.62; $p = 0.136$), the number of lesions > 2 (HR = 1.86; $p = 0.061$), AFP (unit: µg/mol; HR = 1.17; $p < 0.001$), and Child–Pugh score (HR = 5.76, $p = 0.006$; Table 3).

Safety (as Treated) and 30-day Mortality (as Treated)

For complications and 30-day mortality, see Table 4.

Table 3 Univariate and multivariate Cox regression for TTUP, TTP, and OS

Variable	Univariate			Multivariate		
	HR	95%-CI	*P*	HR	95%-CI	*p*
TTUP						
Age (unit: 10 years)	0.99	0.72–1.37	0.963			
Gender (female)	3.31	1.64–6.72	**0.001**	4.21	2.03–8.73	**<0.001**
ITT group (iBT)	0.52	0.30–0.90	**0.021**	0.49	0.27–0.89	**0.019**
Lesion diameter > 5 cm	1.82	0.98–3.39	*0.057*			
Number of lesions > 2	1.77	0.99–3.18	*0.056*	1.80	0.96–3.39	*0.069*
AFP (unit: µg/ml)	1.08	1.00–1.16	**0.038**	1.13	1.05–1.22	**0.001**
Child–Pugh score B	3.91	1.27–12.1	**0.018**	3.81	1.09–13.3	**0.036**
Bilirubin, pretherapeutic > 19 µmol/l[a]	2.03	1.10–3.74	**0.024**			
TTP						
Age (unit: 10 years)	0.74	0.53–1.03	0.070	0.78	0.56–1.08	0.130
Gender (female)	1.80	0.84–3.85	0.128			
ITT group (iBT)	0.49	0.29–0.83	**0.008**	0.49	0.29–0.85	**0.011**
Lesion diameter > 5 cm	1.11	0.60–2.07	0.730			
Number of lesions > 2	1.73	0.98–3.06	*0.060*			
AFP (unit: µg/ml)	1.08	1.00–1.16	*0.058*	1.08	1.00–1.16	*0.063*
Child–Pugh score B	3.33	1.11–10.0	**0.031**	3.12	1.02–9.53	**0.045**
Bilirubin, pretherapeutic > 19 µmol/l[a]	1.86	1.02–3.38	**0.042**			
OS						
Age (unit: 10 years)	1.13	0.79–1.60	0.506			
Gender (female)	2.88	1.35–6.12	**0.006**	3.46	1.59–7.54	**0.002**
ITT group (iBT)	0.61	0.34–1.09	0.097	0.62	0.33–1.16	0.136
Lesion diameter > 5 cm	1.51	0.78–2.93	0.226			
Number of lesions > 2	1.68	0.92–3.07	0.089	1.86	0.97–3.57	*0.061*
AFP (unit: µg/ml)	1.12	1.04–1.21	**0.004**	1.17	1.08–1.26	< 0.001
Child–Pugh score B	6.19	1.90–20.1	**0.002**	5.76	1.65–20.1	**0.006**
Bilirubin, pretherapeutic > 19 µmol/l[a]	3.33	1.72–6.44	**< 0.001**			

Bold values indicate $p < 0.05$

Italic values indicate $p > 0.05$ and $p < 0.07$

[a]Bilirubin was excluded from multivariate analysis because of significant association with Child–Pugh score

Discussion

The intention of this exploratory, randomized, phase II study was to assess the efficacy and safety of iBT in comparison with the standard treatment modality (cTACE) in order to decide whether a multicentric phase III study is justified.

The adjusted hazard ratio of 0.49, as observed both for the primary endpoint TTUP and for the secondary endpoint TTP, is convincing. The adjusted hazard ratio for OS was 0.62 for the entire study group, which also indicates a possible superiority of iBT compared with cTACE. A higher overall survival effect size was observed in patients with BCLC-B (HR = 0.55) and BCLC-C (HR = 0.52), whereas iBT showed no superiority in patients with BCLC-A (HR = 0.92).

In two reported randomized trials of TACE with positive outcome, repetitive TACE was found to have benefit in terms of OS [26, 27]. Consequently, recent TACE trials such as the TACE–sorafenib combination trial SPACE employed TTUP as a secondary endpoint [28]. Some of the conditions preventing TACE—such as the development of PVT or technical failure of TACE indicated by failed uptake of Lipiodol in hypoperfused tumors—do not influence the applicability or the therapeutic effect of iBT [26, 27]. However, these technique-inherent conditions did not apply in the final TTUP analysis.

Results of the PRECISION V study demonstrated better tolerability of DEB-TACE in comparison with conventional TACE [29]. However, since that study did not demonstrate any effect on survival or treatment duration by the choice of the TACE technique, we do not consider that any negative bias was introduced by the use of

Table 4 Adverse events (as treated)

	iBT (n = 120)	cTACE (n = 163)	p
CTCAE ≥ grade III			
BCLC-A	1 (0.8%)	1 (0.6%)	
BCLC-B	2 (1.7%)	5 (3.1%)	
BCLC-C	4 (3.3%)	3 (1.8%)	
Sum	7 (5.8%)	9 (5.5%)	1
CTCAE grade III/IV			
Liver decompensation	3 (2.5%)	3 (1.8%)	
Hepatic abscess treated with drainage and antibiotics	1 (0.8%)	1 (0.6%)	
Partial liver infarction with symptomatic treatment	0	1 (0.6%)	
Cholangitis	0	1 (0.6%)	
Subcapsular hematoma causing hemodynamic shock treated by blood transfusion	1 (0.8%)	0	
Aplastic anemia caused by perchlorate medication	1 (0.8%)	0	
Sum	6 (5.0)	6 (3.7%)	0.767
Mortality within 30 days			
Urinary tract infection and consecutive sepsis	1	0	
Hepatic decompensation	0	1	
Sepsis	0	1	
Brain metastasis leading to status epilepticus	0	1	
Sum	1 (0.8%)	3 (1.8%)	0.640

conventional, Lipiodol-based TACE in our trial (which had been designed before DEB-TACE was established).

In Europe, the recommended application criterion for TACE is BCLC-B with up to 7 points [30]. As outlined previously, favorable results of iBT in our study were evident in patients inside the established range of TACE indications (BCLC-B). In patients with BCLC-A the iBT treatment showed no clinically relevant effect compared with cTACE, with a hazard ratio of 0.83 for TTUP and 0.92 for overall survival. This may have been due to the relatively high efficacy and safety of cTACE in small tumors and small tumor numbers. In contrast, in patients with BCLC-B and BCLC-C a substantial benefit of iBT over cTACE can be assumed regarding the respective hazard ratios for TTUP, TTP, and OS. Assuming an effect size of 0.55, an event probability of 65%, an alpha error of 0.01, and the power to 90%, the sample size required for a phase III study would be 136 per group, respectively.

Because of the exploratory character of this study and the correspondingly small sample size, the confidence intervals of the observed hazard ratios are large and the level of significance was not reached for OS. However, it has to be emphasized that the type I error of a randomized phase II trial is typically high, in the range of 10–20%, to keep patient numbers reasonable, whereas the crucial parameter for a decision to proceed to a phase III trial is the observed effect size [23]. The stratification concerning BCLC stages was not planned prospectively, and thus, the subgroup analyses demonstrating a greater effect in BCLC-B/BCLC-C compared with BCLC-A have to be evaluated critically, especially on account of the small sample size in the subgroups. However, we consider that this stratification may be justified, as the proportional hazard assumption was not satisfied for BCLC stages.

Conclusion

This explorative phase II trial showed a superior outcome of iBT compared with cTACE in HCC, notably in patients with BCLC-B/ BCLC-C and supports proceeding to a phase III trial.

Funding This study was funded exclusively by the University of Magdeburg.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

Financial Support This work was funded exclusively by the University of Magdeburg.

Ethical Considerations The study was conducted in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and ICH-GCP. The study protocol and all study-related documentation were approved by all relevant authorities (Ethics Committee of the Medical Faculty, University of Magdeburg, 44/06).

References

1. Jaeck D, Bachellier P, Oussoultzoglou E, Weber JC, Wolf P. Surgical resection of hepatocellular carcinoma. Post-operative outcome and long-term results in Europe: an overview. Liver Transpl. 2004;10:S58–63.
2. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391:1301–14.
3. Cheng BQ, Jia CQ, Liu CT, et al. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial. JAMA. 2008;299:1669–77.
4. Helmberger T, Dogan S, Straub G, et al. Liver resection or combined chemoembolization and radiofrequency ablation improve survival in patients with hepatocellular carcinoma. Digestion. 2007;75:104–12.
5. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37:429–42.
6. Vogl TJ, Naguib NN, Nour-Eldin NE, et al. Review on transarterial chemoembolization in hepatocellular carcinoma: palliative, combined, neoadjuvant, bridging, and symptomatic indications. Eur J Radiol. 2009;72:505–16.
7. Cucchetti A, Piscaglia F, Cescon M, Ercolani G, Pinna AD. Systematic review of surgical resection vs radiofrequency ablation for hepatocellular carcinoma. World J Gastroenterol. 2013;19:4106–18.
8. Cucchetti A, Piscaglia F, Cescon M, et al. An explorative data-analysis to support the choice between hepatic resection and radiofrequency ablation in the treatment of hepatocellular carcinoma. Dig Liver Dis. 2014;46:257–63.
9. Takayasu K, Arii S, Ikai I, et al. Overall survival after transarterial lipiodol infusion chemotherapy with or without embolization for unresectable hepatocellular carcinoma: propensity score analysis. AJR Am J Roentgenol. 2010;194:830–7.
10. Collettini F, Schnapauff D, Poellinger A, et al. Hepatocellular carcinoma: computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of large (5–7 cm) and very large (> 7 cm) tumours. Eur Radiol. 2012;22:1101–9.
11. Mohnike K, Wieners G, Schwartz F, et al. Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: safety, efficacy, and effect on survival. Int J Radiat Oncol Biol Phys. 2010;78:172–9.
12. Ricke J, Mohnike K, Pech M, et al. Local response and impact on survival after local ablation of liver metastases from colorectal carcinoma by computed tomography-guided high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys. 2010;78:479–85.
13. Ricke J, Thormann M, Ludewig M, et al. MR-guided liver tumor ablation employing open high-field 1.0T MRI for image-guided brachytherapy. Eur Radiol. 2010;20:1985–93.
14. Ricke J, Wust P, Stohlmann A, et al. CT-guided interstitial brachytherapy of liver malignancies alone or in combination with thermal ablation: phase I–II results of a novel technique. Int J Radiat Oncol Biol Phys. 2004;58:1496–505.
15. Ricke J, Wust P, Wieners G, et al. Liver malignancies: CT-guided interstitial brachytherapy in patients with unfavorable lesions for thermal ablation. J Vasc Interv Radiol. 2004;15:1279–86.
16. Tselis N, Chatzikonstantinou G, Kolotas C, Milickovic N, Baltas D, Zamboglou N. Computed tomography-guided interstitial high dose rate brachytherapy for centrally located liver tumours: a single institution study. Eur Radiol. 2013;23:2264–70.
17. Mohnike K, Neumann K, Hass P, et al. Radioablation of adrenal gland malignomas with interstitial high-dose-rate brachytherapy: efficacy and outcome. Strahlenther Onkol. 2017;193:612–9.
18. Mohnike K, Wolf S, Damm R, et al. Radioablation of liver malignancies with interstitial high-dose-rate brachytherapy: complications and risk factors. Strahlenther Onkol. 2016;192:288–96.
19. Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma with portal vein tumor thrombus. Cancer. 2005;104:794–801.
20. Lee SU, Park JW, Kim TH, et al. Effectiveness and safety of proton beam therapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Strahlenther Onkol. 2014;190:806–14.
21. Sugahara S, Nakayama H, Fukuda K, et al. Proton-beam therapy for hepatocellular carcinoma associated with portal vein tumor thrombosis. Strahlenther Onkol. 2009;185:782–8.
22. Mohnike K, Sauerland H, Seidensticker M, et al. Haemorrhagic complications and symptomatic venous thromboembolism in interventional tumour ablations: the impact of peri-interventional thrombosis prophylaxis. Cardiovasc Intervent Radiol. 2016;39:1716–21.
23. Cannistra SA. Phase II trials in journal of clinical oncology. J Clin Oncol. 2009;27:3073–6.
24. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the study of the liver. J Hepatol. 2001;35:421–30.
25. Bruix J, Sherman M. Practice Guidelines Committee AAftSoLD. Management of hepatocellular carcinoma. Hepatology. 2005;42:1208–36.
26. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359:1734–9.
27. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35:1164–71.
28. Lencioni R. Chemoembolization in patients with hepatocellular carcinoma. Liver Cancer. 2012;1:41–50.
29. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33:41–52.
30. Forner A, Gilabert M, Bruix J, Raoul JL. Treatment of intermediate-stage hepatocellular carcinoma. Nat Rev Clin Oncol. 2014;11:525–35.

Veröffentlichung 16

Needle track seeding in hepatocellular carcinoma after local ablation by high-dose-rate brachytherapy: a retrospective study of 588 catheter placements.

Damm R, Zörkler I, Rogits B, Hass P, Omari J, Powerski M, Kropf S, Mohnike K, Pech M, Ricke J, Seidensticker M.

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Original paper

Needle track seeding in hepatocellular carcinoma after local ablation by high-dose-rate brachytherapy: a retrospective study of 588 catheter placements

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Abstract

Purpose: Needle track seeding in the local treatment of hepatocellular carcinoma (HCC) is not yet evaluated for catheter-based high-dose-rate brachytherapy (HDR-BT), a novel local ablative technique.

Material and methods: We report a retrospective analysis of 100 patients treated on 233 HCC lesions by HDR-BT (using 588 catheters in total). No needle or catheter track irradiation was used. Minimum required follow-up with imaging was 6 months. In case of suspected needle track seeding (intra- and/or extrahepatic) in follow-up, image fusion of follow-up CT/MRI with 3D irradiation plan was used to verify the location of a new tumor deposit within the path of a brachytherapy catheter at the time of treatment.

Results: We identified 9 needle track metastases, corresponding to a catheter-based risk of 1.5% for any location of occurrence. A total of 7 metastases were located within the liver (catheter-based risk, 1.2%), and 2 metastases were located extrahepatic (catheter-based risk, 0.3%). Eight out of 9 needle track metastases were successfully treated by further HDR-BT.

Conclusions: The risk for needle track seeding after interstitial HDR-BT of HCC is comparable to previous reports of percutaneous biopsies and radiofrequency ablation (RFA), especially in case of extrahepatic needle track metastases. To compensate for the risk of seeding, a track irradiation technique similar to track ablation in RFA should be implemented in clinical routine.

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Key words: hepatocellular carcinoma, local ablative treatment, needle track seeding.

Purpose

Hepatocellular carcinoma (HCC) is a primary liver tumor most often found in patients with liver cirrhosis and/or viral hepatitis. Its incidence has increased over the last years worldwide [1]. Beneath surgical resection, local ablative (e.g., radiofrequency ablation – RFA, microwave ablation – MWA) and loco-regional (e.g., transarterial chemoembolization – TACE) treatments are favored for early to intermediate stage of HCC. However, these treatments may not be suitable for every patient due to technical restrictions [2,3,4]. Thermal ablation techniques have their limitations, especially in location close to vulnerable structures (e.g., bile ducts) and lesion size of 3.5 to 4 cm, while loco-regional techniques require sufficient, vascular access for the application of embolic agents, showing lack in local control if tumor nodules exceed a size of 5 to 7 cm [5,6]. Thus, computed tomography (CT)-guided high-dose-rate brachytherapy (HDR-BT) as a form of catheter-based radiotherapy is a promising treatment option for tumors not accessible for thermal ablation techniques as well as an alternative to TACE. By inserting an Iridium 192 source through percutaneously applied catheters, interstitial brachytherapy has no technical restrictions in lesion size to deliver potentially ablative doses, and can be employed close to central structures [7,8]. In a series of studies, the safety and effectiveness of HDR-BT has already been

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demonstrated, suggesting a potential as a bridging therapy to liver transplantation in addition to radiofrequency ablation or transarterial chemoembolization [9].

The risk of spreading malignant cells during diagnostic and therapeutic methods have been reported for liver biopsy and thermal ablation with heterogeneous results, also varying by the utility of needle track ablation [10,11,12,13]. As the catheter placement for HDR-BT comprises an initial puncture (including possible corrections of the needle position) and insertion of catheter sheets in Seldinger's technique, a corresponding risk of dislocating tumor cells through manipulation should be assumed.

The risk of needle track seeding after HDR brachytherapy, particularly in case of the potential utility as a bridging treatment for liver transplantation in early stage HCC, should be further investigated. On the other side, patients with larger tumor volumes in intermediate stage of the disease might have an increased risk for needle track seeding, as more catheter placements are required for a sufficient dose distribution [14]. In this retrospective study, we report needle track seeding after HDR brachytherapy in a series of 100 patients, with a total of 588 catheter placements for local ablation of 233 HCC lesions. No catheter or needle track irradiation had been used in these patients.

Material and methods

Eligibility criteria and patient cohort

We retrospectively analyzed patients who underwent interstitial HDR brachytherapy for HCC between 2006 and 2012. All lesions were previously proven either by core needle biopsy or by matching the non-invasive criteria of HCC in CT or magnetic resonance imaging (MRI) [15], according to the Clinical Practice Guidelines of the European Association for the Study of the Liver (EASL) released in 2012 [16].

100 patients (83 males, 17 females), with 233 HCC nodules and a total of 588 catheter placements met the inclusion criteria (see section follow-up). The average age at the time of intervention was 68 ± 8.1 years (44-82 years). Nearly all patients had an underlying liver cirrhosis (n = 98), mainly caused by alcohol consumption (n = 28) or viral hepatitis (n = 22). Infrequent causes of cirrhosis were non-alcoholic steatohepatitis (n = 8) and hemochromatosis (n = 2). In all other cases, the etiology of cirrhosis was cryptogenic (n = 38).

Only a minority of patients presented with extrahepatic disease including lymphatic (n = 5) or distant metastases (n = 5). A summary of patient and treatment characteristics is presented in Table 1.

Table 1. Patient and treatment characteristics and analysis on influencing factors for needle track seeding

Variable	% (*N*) or mean ± SD	Patient-based *p*	Lesion-based *p*	Catheter-based *p*
Male/female	83% (83)/17% (17)	0.66	0.49	0.33
Age (years)	68.0 ± 8.1	0.26	0.21	0.37
Liver cirrhosis	98% (98/100)			
hemochromatosis	2% (2/98)	1.0		
viral hepatitis	22% (22/98)	1.0		
ASH	29% (28/98)	0.99		
NASH	8% (8/98)	0.99		
other	39% (38/98)			
HCC grading	62% (62/100)	0.54	0.23	0.3
well	39% (24/62)			
moderate	55% (34/62)			
poor	6% (4/62)			
Concomitant sorafenib treatment	22% (22/78)	0.6	0.96	0.62
Pseudo-capsular HCC	8% (18/233)	0.98		
Lesion size (cm)	3.3 ± 2.6	0.2	0.78	0.09
Ablation dose (Gy)	16.5 ± 11.6	0.65	0.7	0.59
Overpenetration (per catheter)	9% (53/588)	0.23	0.69	
Catheter insertion lengths (cm)				
/patient	74.8 ± 57.4	0.94		
/lesion	32.1 ± 37.4		0.78	
/catheter	12.7 ± 31.2			0.75

HDR brachytherapy technique

In order to place an Iridium 192 source directly in the HCC lesions, irradiation catheters must be inserted into the tumor. The access for a soft catheter is accomplished by a percutaneous puncture with an 18 Ga coaxial needle under image guidance (CT or open MRI fluoroscopy) and subsequent insertion of an angiographic catheter sheet in Seldinger's technique. The irradiation catheter is then placed inside the catheter sheath and fixed by a single suture. For planning purposes, diagnostic imaging (e.g., contrast enhanced CT) is performed after complete catheter placement. Afterwards, a three-dimensional treatment plan is generated based on diagnostic imaging data acquired following catheter placement. Generally, the preferred surrounding dose for HCC is 15 Gy. After successful delivery of the desired dose in a single fraction, the catheters and sheaths are removed leaving absorbable gelatin sponge in the track. Concomitant conscious sedation is achieved by individual administration of fentanyl and midazolam. A further description of irradiation technique and concomitant treatment is presented elsewhere [17].

Follow-up

All eligible patients required a follow-up consisting of CT or MRI at least 3 and 6 months after therapy, with a dynamic contrast-enhanced scan protocol including arterial, portal venous, and late venous phase. Any new intrahepatic lesion with a diameter of at least 1 cm and arterial enhancement with venous wash out was defined as an intrahepatic recurrence of HCC, while clear tumor growth outside the liver was sufficient for the definition of extrahepatic lesions [16].

Subsequent therapies in the follow-up period included sorafenib (n = 22), transarterial chemoembolization (n = 18), Y90 radioembolization (n = 4), and radiofrequency ablation (n = 4).

Imaging analysis

We determined the primary tumor size, number and location of metastases, the total length of each catheter from the skin to the tip as well as 'over-penetration' of the tip beyond the HCC lesion.

As a first step, the available image data sets were evaluated for the probability of needle tract seeding according to the following definitions: 1) Temporal causality: needle track seeding should be diagnosed after therapy within a reasonable timeframe of 2 years; 2) Local causality: needle tract seeding had to be situated around a prior catheter track within a margin of 1 cm.

In a second step, the suspected needle track metastases had to be objectively verified. Amira® 3.x was applied for the fusion of CT/MRI and irradiation treatment plans. Overlay images were generated to determine the exact position of the suspected metastases in relation to the prior catheter location.

As a novel approach, we assessed both, extrahepatic and intrahepatic seeding. An example of an image fusion data set is provided in Figure 1.

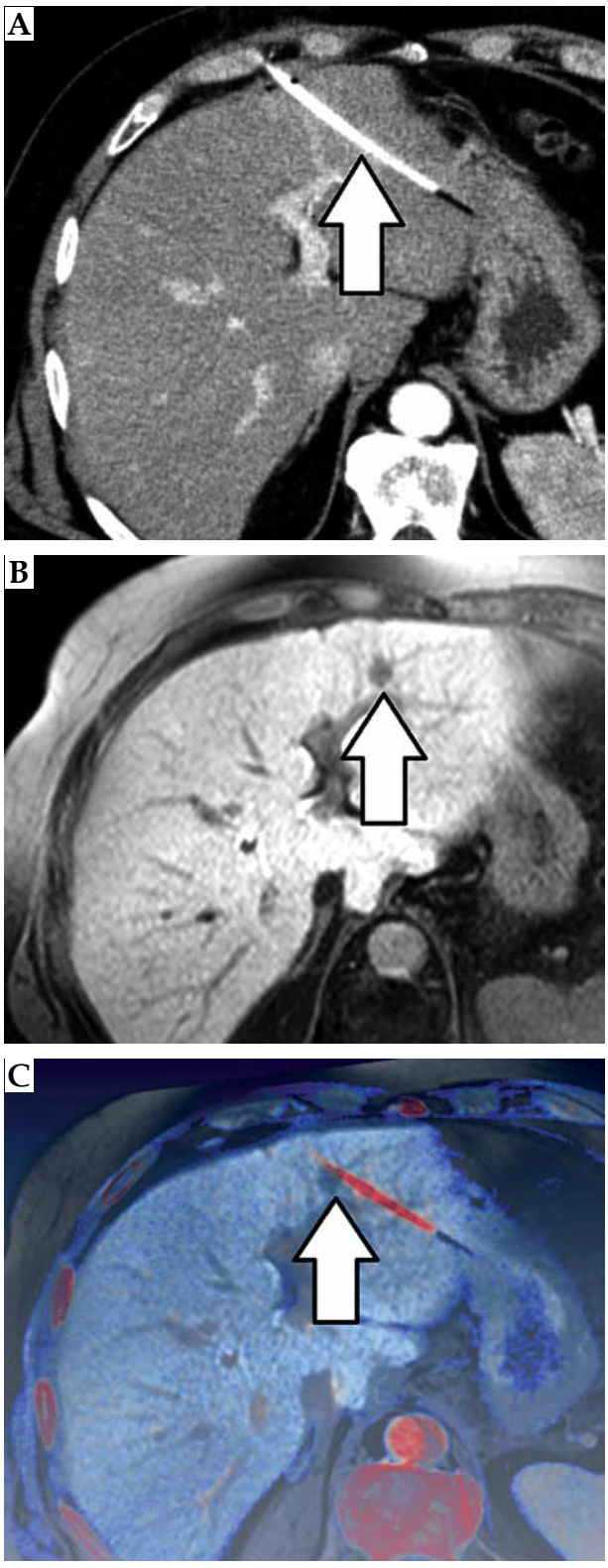

Fig. 1. Image fusion data set: peri-interventional CT showing HDR brachytherapy catheter (arrow, **A**), follow-up MRI suspecting a needle track lesion (arrow, **B**), axial image fusion of follow-up MRI and planning CT of HDR brachytherapy confirming the origin of the new lesion within the former path of the brachytherapy catheter (arrow, **C**)

Statistical analysis

We collected technical data of the irradiation plan and documented possible risk factors such as patient demographics, histological grading, and imaging features.

The statistical analysis of the data was conducted by using the statistical software SPSS® and SAS®. Differences between variables were examined using Student's *t*-test for metric variables and Chi-Square test for frequencies. The survival analysis was performed according to Kaplan-Meier method, the statistical significance was determined using log-rank test. The influence of potential risk factors on the occurrence of needle track metastases was calculated using a generalized linear mixed model. All tests were performed two-sided, a *p*-value of $p \leq 0.05$ was considered statistically significant.

Results

Patient and treatment characteristics

In our cohort of 100 patients, a total of 233 HCC lesions were treated. In 62 patients, histological reports were available with 38.7% ($n = 24$) being well differentiated, 54.8% ($n = 34$) being moderately differentiated, and 6.5% ($n = 4$) being poorly differentiated tumors. Pseudo-capsular HCC were present in 18 out of 233 lesions (7.7%). 22 patients (22%) received concomitant therapy with sorafenib.

In all patients, thermal ablation was technically not favorable related to either tumor size (exceeding 3 cm) or tumor location (proximity to liver hilum or adjacent gastrointestinal structures) of at least one lesion.

The median follow-up was 15.7 months (range, 6-70.2 months). Within the observation period, 67 patients developed a tumor progression with a median progression-free survival of 7.0 months. Median overall survival of all patients was 20.0 months. A summary of patient and treatment characteristics is presented in Table 1.

Catheter-based analysis

A total number of 588 catheters were placed within 100 patients. The mean insertion length of a single catheter was 12.7 ± 31.2 cm (range, 5.7-25.4 cm). Four catheters were too remote in relation to the target lesion and were not used for irradiation (0.7%). However, these lesions were treated in the same session with more precisely placed catheters. A total of nine needle track metastases were identified yielding an incidence of 1.5% per catheter placement. Seven out of nine seeding metastases were located within the liver (catheter-based risk for intrahepatic seeding, 1.2%). Two metastases occurred within the peritoneal cavity in the location of a former catheter path (catheter-based risk for extrahepatic seeding, 0.3%).

Lesion-based analysis

A total of 233 HCC lesions were treated. The mean diameter of HCC nodule was 3.3 ± 2.6 cm (range, 1.0-16.6 cm) requiring a mean number of 2.6 catheters per lesion to ensure a sufficient dose application. The mean applied radiation dose at the tumor rim was 16.5 ± 11.6 Gy. The mean sum of in-body catheter length per lesion was 32.1 ± 37.4 cm (range, 5.9-247.0 cm). Over-penetration of HCC nodule was found in 53 cases (9.0%), with a mean over-penetration length of 1.2 cm (range, 0.1-2.8 cm). The cumulative frequency of needle track metastases per treated tumor was 3.9% (intrahepatic location, 3.0%; extrahepatic location, 0.9%).

Patients-based analysis

In our cohort of 100 patients, an average number of 5.9 catheters were placed per patient leading to a mean total in-body catheter length of 74.8 ± 57.3 cm (range, 8.6-288.8 cm). Imaging analysis revealed needle track metastases in 9 patients. The mean time of occurrence of needle track seeding was 5.5 months (range, 4.8-6.2 months).

Risk assessment

Needle track seeding occurred in a median time interval of 5.5 months (range, 4.8-6.2 months). No increased risk was found for the tumor grading, age, and sex.

In a catheter-based analysis, we found more frequent seeding in smaller HCC lesions ($p = 0.09$). Liver cirrhosis and underlying etiology had no significant influence on the development of needle track seeding; the same was seen for pseudo-capsular HCC. Treatment-related parameters such as catheter insertion lengths, over-penetration of the lesion (i.e., with the possibility of dislocating tumor cells beyond the lesions into the liver parenchyma), and applied dose as well as concomitant treatment with sorafenib, demonstrated no significant influence.

Of note, 8 out of 9 seeding metastases were successfully treated by further HDR-BT directly after their occurrence. In one case, needle track metastasis occurred parallel to systemic progression at other sites and needed systemic therapy with sorafenib.

Median overall survival was 25.0 months in patients with needle track vs. 20.0 months in patients without ($p = 0.86$, log-rank test). The overall results of the risk factor analysis are included in Table 1.

Discussion

We were able to calculate the risk for tumor seeding after local ablation of HCC by catheter-based radiotherapy for both intrahepatic and extrahepatic locations, with an analysis of catheter-, lesion-, and patient adjusted frequencies. No track irradiation had been used in these patients.

Needle track seeding in local ablation

Needle track seeding in HCC is known to occur after diagnostic biopsies and local ablative procedures such as radiofrequency or microwave ablation. Stigliano *et al*. reported a meta-analysis of diagnostic and therapeutic interventions in 2007, with an overall frequency of 1.27% after liver biopsy and/or local ablation with extrahepatic needle track metastases [11].

Initial reports of seeding in up to 12.5% of patients after RFA illustrated the demand of track ablation tech-

niques [18]. Similarly, recent reports after RFA and MWA using track ablation depict low seeding rate of 0.61% to 1.6% [13,19]. However, all these studies have focused on extrahepatic seeding only; intrahepatic seeding was not evaluated to differentiate tumors seeding from *de novo* HCC due to technical limitations.

Our recent study identified a cumulative (extrahepatic and intrahepatic) catheter-based risk for seeding of 1.5% (without track ablation technique), which is comparable to reported seeding risk after thermal ablation using track ablation or even lower, considering that literature focusses on extrahepatic seeding only.

Due to the need of multiple catheters in larger HCC lesions (mean lesion diameter in our cohort: 3.3 ± 2.6 cm; range, 1.0-16.6 cm), the cumulative lesion-based seeding risk is as high as 3.9%. Theoretically, the seeding risk is still comparable to thermal ablation techniques, considering the need for multiple probes/multiple positions and in RFA or MWA ablation for the treatment of larger tumors.

Extrahepatic seeding

As stated above, our data indicates that the risk for extrahepatic seeding (0.2% per catheter) after HDR brachytherapy is comparable or even lower than after thermal-based ablative techniques (0.61-1.6%). Furthermore, our data supports findings previously published by Denecke *et al*. who utilized HDR brachytherapy in the pre-transplant setting and found no extrahepatic recurrence due to seeding in their smaller group of patients undergoing subsequent liver transplantation [9]. In fact, only a minority of seeding metastases occurred outside the liver in our cohort (0.2% per catheter). Assuming a tumor size and tumor number within transplant criteria for HCC, the lesion-based and patient-based risk should be equal or only slightly increased in those patients as compared to the catheter-based risk supporting the findings of Denecke *et al*. Both, the work of Denecke *et al*. and our results support the use of HDR brachytherapy as bridging for transplant, at least in tumors with an unfavorable location for RFA or TACE.

In case of larger or multilocular HCC outside transplant criteria, multiple catheter placements in HDR brachytherapy are usually necessary, resulting in a higher seeding rate (e.g., 0.9% in lesion-based analysis). Theoretically, several needle positions would have been required for a complex thermal ablation in those patients. Thus, the cumulative risk (i.e., lesion- and catheter-based risk) for track seeding seen in our study can be assumed to be comparable to a cumulative risk resulting from multiple ablation positions in RFA/MWA [11,20,21].

Intrahepatic seeding

Unfortunately, many studies still neglect the possibility of intrahepatic seeding, probably as the differentiation between intrahepatic seeding metastases and tumor progression is difficult [12]. We applied a novel approach of image fusion for the identification of intrahepatic seeding, leading to the confident identification of lesions, which most likely derive from track seeding. All these lesions are omitted by the extrahepatic definition of seeding in most studies. In fact, intrahepatic needle track metastases were more frequent as compared to extrahepatic needle track metastases with a catheter-based risk of 1.3%. This is easily explainable, since the penetration depth within the liver parenchyma is usually longer than the thickness of the abdominal wall.

The higher rate of intrahepatic seeding as compared to extrahepatic seeding in our analysis, along with the focus on extrahepatic-only seedings in literature, suggests that seeding (intrahepatic plus extrahepatic) after thermal ablation or biopsy might be more frequent, but data to further elucidate that matter is not available. However, this might pose a clinical impact for treatment decision making and should be a subject for further investigation. Furthermore, techniques to decrease the seeding rate after HDR brachytherapy were not applied in the study population. As a consequence of our analysis, we established a procedure similar to needle track ablation by radiation of the path of the catheter during the withdrawal of the Iridium 192 source, with a mean dose of 10 Gy in up to 2-3 mm depth. Taking RFA and MWA as an example, the introduction of track ablation techniques resulted in drastically lower rate of (extrahepatic) seeding (from 12.5% to 0.61-1.6%; see above), indicating a significant influence of track ablations techniques to control tumor seeding in local ablations of HCC. We believe that this applies also to HDR brachytherapy.

Beside this assumed influencing factor on track seeding, none of the evaluated variables within the study revealed a significant influence on the rate of track seeding on a catheter-, lesion-, and patient-based analysis, as these were in particular sex, age, etiology of liver disease, grading of the HCC, evidence of a tumor pseudo-capsular, size of the targeted lesion, in situ catheter length, over-penetration of the targeted lesion, ablation dose, and concomitant systemic treatment. Only the size of targeted lesion showed a tendency to significantly influence track seeding (in the patient-based analysis, $p = 0.09$), with a higher rate of track seeding in smaller lesions. It can be hypothesized that more manipulations (i.e., needle passes to enable a sufficient catheter placement) are needed in smaller lesions. Quantitative or semi-quantitative information on needle manipulations during the intervention were not available in this study making further clarification of this hypothesis impossible. However, since this finding was only evident on a patient-based analysis but not on a lesion- or catheter-based analysis, stochastic effects are the most probable cause.

Limitations

The limitations of this analysis are those inherent to a retrospective analysis. Although study format was retrospective, the data (clinical data, treatment-related data) were obtained from a prospectively managed database, in which all patients who undergo a local or loco-regional treatment at our department are electronically filed using standardized reporting forms for treatment and follow-up visits. Additionally, treated patient undergo

a standardized follow-up including imaging (at our institution) every three months, which diminishes a possible bias derived from inconsistent image follow-up intervals and inconsistent imaging protocols. However, a patient selection bias cannot be ruled out.

As pointed out in the section above, we were not able to evaluate systematically the incidence of needle manipulations during the interventions, which could have an influence on the risk of track seeding, since the number of possible tumors passes increases. However, misplacements of the needle during the intervention usually occur outside the tumor (i.e., in the liver parenchyma without risk for seeding), a believed position within the tumor (although position might not be perfect for treatment) entail the exchange to the brachytherapy catheter by standard operating procedure in order to prevent seeding. Thus, we believe that the possible influence of needle manipulations during the interventions is too small to neglect.

Finally, the differentiation between iatrogenic track seeding and de novo HCC is still a challenge that might influence the analysis. Since all possible track seeding metastases were verified in their origin by precise image registration of the follow-up imaging with the final imaging after placement of the brachytherapy catheters, we can rule out an underestimation of the frequency of treatment-associated track seeding. Only a risk for an overestimation of the frequency of new metastases related to the previously performed local ablation is possible but is regarded as acceptable from a clinical and scientific perspective.

Conclusions

The technique of percutaneous catheter placement for HDR brachytherapy in HCC is generally not associated with an elevated risk of needle track metastases as compared to biopsy or RFA/MWA, especially in extrahepatic seeding. In fact, data indicates a lower risk for track metastases after HDR brachytherapy as compared to biopsy and thermal-based ablation techniques, although HDR brachytherapy was conducted without a track ablation technique in this study.

To further reduce the risk of seeding along the catheter path, track irradiation in HDR brachytherapy should be implemented in daily practice.

Disclosure

Authors report no conflict of interest.

References

1. Schütte K, Kipper M, Kahl S et al. Clinical characteristics and time trends in etiology of hepatocellular cancer in Germany. *Digestion* 2013; 87: 147-159.
2. Han K, Kim JH. Transarterial chemoembolization in hepatocellular carcinoma treatment: Barcelona clinic liver cancer staging system. *World J Gastroenter* 2015; 21: 10327-10335.
3. Feng K, Ma KS. Value of radiofrequency ablation in the treatment of hepatocellular. *World J Gastroenterol* 2014; 20: 5987-5998.
4. Tanaka M, Ando E, Simose S et al. Radiofrequency ablation combined with transarterial chemoembolization for intermediate hepatocellular carcinoma. *Hepatol Res* 2014; 44: 194-200.
5. Terzi E, Piscaglia F, Forlani L et al. TACE performed in patients with a single nodule of hepatocellular carcinoma. *BMC Cancer* 2014; 14: 601.
6. Yang W, Yan K, Wu GX et al. Radiofrequency ablation of hepatocellular carcinoma in difficult locations: Strategies and long-term outcomes. *World J Gastroenterol* 2015; 21: 1554-1566.
7. Mohnike K, Wieners G, Schwartz F et al. Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: safety, efficacy, and effect on survival. *Int J Radiat Oncol Biol Phys* 2010; 78: 172-179.
8. Collettini F, Singh A, Schnapauff D et al. Computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of metastases adjacent to the liver hilum. *Eur J Radiol* 2013; 82: e509-514.
9. Denecke T, Stelter L, Schnapauff D et al. CT-guided Interstitial Brachytherapy of Hepatocellular Carcinoma before Liver Transplantation: An Equivalent Alternative to Transarterial Chemoembolization? *Eur Radiol* 2015; 25: 2608-2616.
10. Cabibbo G, Craxi A. Needle track seeding following percutaneous procedures for hepatocellular carcinoma. *World J Hepatol* 2009; 1: 62-66.
11. Stigliano R, Marelli L, Yu D et al. Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC. *Cancer Treat Rev* 2007; 33: 437-447.
12. Francica G. Needle track seeding after radiofrequency ablation for hepatocellular carcinoma: prevalence, impact, and management challenge. *J Hepatocell Carcinoma* 2017; 4: 23-27.
13. Yu J, Liang P, Yu XL et al. Needle track seeding after percutaneous microwave ablation of malignant liver tumors under ultrasound guidance: analysis of 14-year experience with 1,462 patients at a single center. *Eur J Radiol* 2012; 81: 2495-2499.
14. Collettini F, Schnapauff D, Poellinger A et al. Hepatocellular carcinoma: computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of large (5-7 cm) and very large (> 7 cm) tumours. *Eur Radiol* 2012; 22: 1101-1109.
15. Bruix J, Sherman M, Llovet JM et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; 35: 421-430.
16. European Association for The Study Of The L, European Organization For R, Treatment Of C. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; 56: 908-943.
17. Ricke J, Wust P. Computed tomography-guided brachytherapy for liver cancer. *Semin Radiat Oncol* 2011; 21: 287-293.
18. Llovet JM, Vilana R, Bru C et al. Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. *Hepatology* 2001; 33: 1124-1129.
19. Zhong-Yi Z, Wei Y, Kun Y et al. Needle track seeding after percutaneous radiofrequency ablation of hepatocellular carcinoma: 14-year experience at a single center. *Int J Hyperthermia* 2017; 33: 1-20.
20. Shirai K, Tamai H, Shingaki N et al. Clinical features and risk factors of extrahepatic seeding after percutaneous radiofrequency ablation for hepatocellular carcinoma. *Hepatol Res* 2011; 41: 738-745.
21. Silva MA, Hegab B, Hyde C et al. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. *Gut* 2008; 57: 1592-1596.

Veröffentlichung 17

Small renal carcinoma: the “when” and “how” of operation, active surveillance, and ablation

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Review paper

Small renal carcinoma: the "when" and "how" of operation, active surveillance, and ablation

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Abstract

Small, locally restricted renal cell carcinoma less than 4 cm in size should ideally be removed operatively by nephron-sparing tumour enucleation (partial kidney resection). In an increasingly elderly population, there is a growing trend toward parallel incidence of renal cell carcinoma and chronic renal insufficiency, with the latter's associated general comorbidities. Thus, for some patients, the risks of the anaesthesia and operation increase, while the advantage in terms of survival decreases. Transcutaneous radio-frequency ablation under local anaesthesia, transcutaneous afterloading high-dose-rate brachytherapy under local anaesthesia, and percutaneous stereotactic ablative radiotherapy may offer a less invasive alternative therapy. Active surveillance is to be regarded as no more than a controlled bridging up to definitive treatment (operation or ablation), while watchful waiting, on account of the lack of prognostic relevance and the symptomatology of renal cell carcinoma, with its comorbidity-related, clearly reduced life expectancy, does not involve any further diagnostic or therapeutic measures.

Key words: renal cell carcinoma, small renal tumour, active surveillance, ablation, focal therapy.

Introduction

Renal cell carcinoma (RCC) is one of the 10 most common malignomas. Its increasing incidence results from increased age, morbidity, and noxa, as well as from the increasingly widespread use of modern imaging techniques [1]. In parallel, there is an increasing frequency of comorbidities (with negative influence upon oncological disease progression) and chronic renal insufficiency (associated *a priori* with poorer life expectancy). Early-stage RCC is usually discovered by chance [2]. This epidemiological development and the possible side effects of immediate renal tumour resection call for alternative therapies.

"Small" renal tumour

RCC in early stages is usually asymptomatic and is therefore usually discovered by chance, in screening or in the diagnosis of other disorders. Empirically, any solid growth on the kidney must arouse suspicion of RCC. If imaging reveals typical criteria for suspicion of malignant growth, then the presence of RCC must be suspected. According to current guidelines, this would comprise a sufficient indication for surgical removal of the tumour, without prior confirmation by biopsy and histology, as long as there are no contra-indications for operation by intubation narcosis [1,2].

The term "small renal tumour" is primarily an image-based morphological description of a solid growth

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Authors' contribution:
A Study design · **B** Data collection · **C** Statistical analysis · **D** Data interpretation · **E** Manuscript preparation · **F** Literature search · **G** Funds collection

on the cortical renal parenchyma, without any assessment of the nature, malignity, or exact location. In English-speaking countries this is termed "small renal mass" (SRM) when its diameter is 3 cm or less [3]. In continental Europe, a solid growth in the renal parenchyma extending up to 4 cm is referred to as a "small renal tumour" (German *kleiner Nierentumor*); this is analogous to the T category "cT1a, cN0, cM0; stage 1" in the 2017 UICC (*Union Internationale Contre le Cancer*) classification for locally restricted non-metastasised RCC [1-5]. The prognostic limit of 4 cm for T1a is of historical origin and does not agree with recent results according to which the rates of growth and metastasis increase exponentially above a tumour size of 3 cm. Experience has been gathered in clinical studies up to a tumour size of 3 cm [2].

Numerous studies of the progress of T1a small renal tumours have shown a relatively slow annual growth, with a very low rate of metastasis in the first five years, but it must be noted that these results include a significant number of uncertainly diagnosed or benign tumours and various RCC subtypes [6,7]. Up to 20-30% of SRMs turn out in histological analysis to be benign oncocytomas [8]. Chawla *et al.* performed a meta-analysis for the subgroup of biopsy-confirmed pT1a RCCs (n = 120) with a median tumour size of 2.48 cm (range 1.7-4.0 cm); they found a median annual growth rate of 0.35 cm (range 0.42-1.6 cm) in an average observation period of 30 (range 25-39) months [9]. Jewett *et al.* analysed 101 biopsy-confirmed pT1a RCCs, finding a progression rate of 0.13 cm/year and a metastasis rate of 1.1% per year in a median observation period of 28 months [10]. Thompson *et al.* reported a metastasis rate of 0.0013% (1/720) for RCC smaller than 3 cm in a median observation period of 2.8 years. They found an increase in metastasis rate of 24% for each 1 cm tumour size increase [11]. Thus, tumour size is one of the most important prognosis factors for the course of disease and for metastasis.

In early stages the localised RCC mainly displaces other tissue and to some extent permeates it. Often, a peritumoral pseudocapsule ("surgical capsule") arises through compression of healthy cells in the surrounding tissue and of peripheral tumour cells [7]. This pseudocapsule, on average only 0.5 mm thick, is individually formed and can vary from a complete or incomplete pseudocapsule with or without tumour infiltration through to a completely absent pseudocapsule [12,13]. Sometimes microscopic satellite tumours are found in the immediate vicinity of the macroscopic tumour [14].

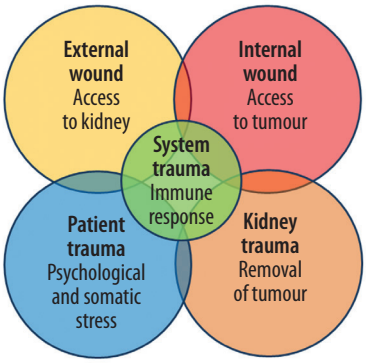

Figure 1. Procedures and their respective degrees of invasiveness, to be considered in the choice of therapy

Biopsy

Confirmation of a renal tumour by biopsy and histological analysis, prior to possible surgical treatment, is not routinely recommended, because it does not affect the choice of treatment and also because of residual diagnostic uncertainty. According to the S3 guidelines, biopsy should be performed in cases of unclear solid growths on the kidney when this might affect the choice of therapy, when active surveillance (AS) is being considered, or when ablation is due to be performed [1]. For solid tumours a double coaxial cylinder biopsy for histological analysis (18G needle), outside any region of possible central tumour necrosis, is recommended. Despite the relatively high sensitivity and specificity of the biopsy-based test for a solid RCC, there is still a high rate (up to 20%) of false negatives or uninformative samples. In a meta-analysis of 1330 small (2.4-4.1 cm diameter) renal tumour biopsies, directed by coaxial computed tomography, the accuracy of targeting was 78-100% and the correct assignment of malignity was 86-100%; whereby the accuracy was 86-100% for the histological RCC subtype and 46-76% for the gradings [15]. A negative biopsy (finding of normal parenchyma) should therefore be followed by a repeat biopsy if this is required for support of the choice of therapy. A further limitation of diagnosis by biopsy to determine the exact tumour entity is the intratumoural biological heterogeneity of the RCC, although this can be less clearly visible for smaller tumours [16]. Oncocytomas, which are fundamentally classified as benign, are in some cases difficult to distinguish from oncocytically differentiated RCC; sometimes this can only be done by histochemistry, and it appears possible that such tumours can degenerate to carcinomas [17].

The "inoperable" patient

From a purely surgical, technical standpoint, every locally restricted kidney tumour and every patient affected is in principle operable. A general, or functional inoperability arises through severe comorbidity that renders impossible either the intubation anaesthesia with muscle relaxants or the necessary peri-operative management, or that makes the immediate or subsequent risk for the patient unjustifiably high. Therefore, for every patient, one must perform a critical risk–benefit analysis of any curative treatment, be it by tumour resection or by interventional ablation. This consideration must take account of the degree of invasiveness – individually and overall – of the various measures to be taken (Figure 1).

The term "minimally invasive" for invasive procedures is frequently narrowed to refer only to the external access (external wound). However, in the case of kidney tumour, the internal access to the tumour itself and the damage inflicted collaterally on the renal parenchyma have a major influence upon the risk of perioperative complications and the patient's subsequent quality of life. Here the patient's age and general condition are particularly important for the prognosis. The incidence of renal tumour peaks in the seventh decade, so most of those affected are elderly ('younger old', 65-74 years; 'mid-old', 75-84 years; 'old-old', ≥ 85 years; definitions by the International Society of Geriatric Oncology [SIOG] [18,19]). A structured geriatric assessment (Barthel Index, Mini-Mental-State Test, Tinetti Test) and a systematic recording of comorbidities (Charlson Comorbidity Index, American Society of Anaesthesiologists [ASA] Score, degree of sarcopaenia, Eastern Cooperative Oncology Group [ECOG] status) allow individual decision-making, and in about half of all cases they lead to a change in therapy decision [20-24] by consideration of the patient's mobility, competence in everyday situations, resilience, and life expectancy.

Hand in hand with the patient's age and morbidity, there is an increasing risk of peri- and post-operative complications and, moreover, a risk of death due to comorbidities. Thus, the complication rate in partial renal resection among patients under 50 years of age is around 30% and among 80-year-olds it is around 50%. In the presence of relevant comorbidities (Charlson index ≥ 2) the complication rate in partial renal resection and tumour nephrectomy is six times higher than in their absence [25]. Among the over-80s severe intervention-related complications occur in 35% of cases (Clavien-Dindo ≥ III), with a mortality of around 3% [26]. Lane *et al.* investigated 537 patients with SRM; for those aged ≥ 75 years he found no significant difference in survival between AS and surgical treatment (partial renal resection and tumour nephrectomy). In that survey 28% (n = 148) of the patients died within the median follow-up period of ca. four years, whereby 24% of the deaths had causes other than progressive, metastasising RCC; most were due to cardiovascular disorders [27]. Likewise, Sun *et al.* found no survival advantage of resecting small RCCs as regards carcinoma-specific mortality among patients aged over 75 years or among those with a Charlson Comorbidity Index of 2 or above [28,29].

The degree of collateral damage to healthy peritumoral renal parenchyma caused by invasive treatment is correlated with the risk of chronic renal insufficiency or its worsening and with the associated cardiovascular comorbidity, with consequent reductions in the patient's life expectancy and quality [30,31]. The development of kidney-preserving, nephron-sparing therapies is therefore an important goal. If renal tumour enucleation, enucleoresection, and sparing partial renal resection all appear unpromising and nephrectomy is considered highly risky, then for patients with chronic renal insufficiency, with only one kidney or with metachronic, multilocular RCC growth patterns (imperative indication for kidney preservation) ablative treatment should be considered as an alternative to resection (Figure 2).

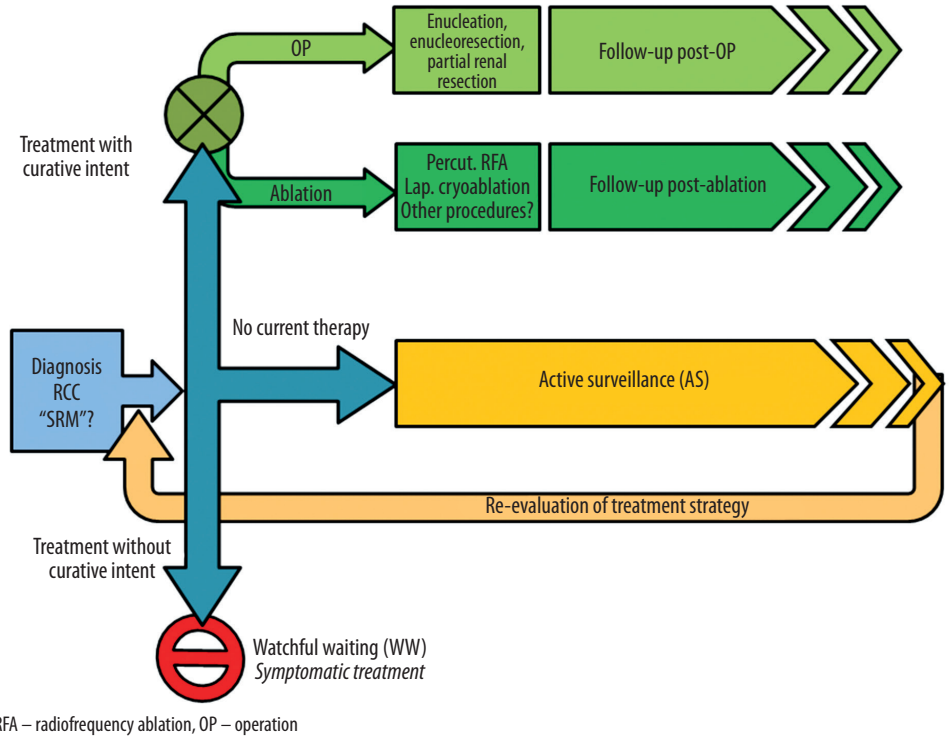

Figure 2. Decision algorithm for treating small renal mass (SRM) or renal-cell carcinoma (RCC)

Damage to healthy renal parenchyma caused by invasive treatment is correlated with the risk of chronic renal insufficiency. Decisive factors for the success and for the complication rate are also the position and the size of the renal tumour. Anatomical classification systems, such as the PADUA (preoperative aspects and dimensions used for anatomical classification) score, the R.E.N.A.L. (radius, exophytic/endophytic, nearness to collecting systems or sinus, anterior/posterior, and location relative to polar lines) score, the CIndex, and the ABLATE algorithm, are intended to be used as aids to decide the type of treatment (operation and operative method; ablation and ablation method; AS) [32,33].

For patients with a reduced life expectancy – on the basis, e.g., of advanced age or very severe comorbidity – following the course of an asymptomatic tumour (discovered by chance) would mean psychological and physical stress; this would be unnecessary and would have no therapeutic value. For patients of this kind, a strategy of waiting, without directed diagnoses or therapy, should be considered. This "watchful waiting" or "wait-and-see" procedure differs fundamentally, in indication and in conduct, from AS (Figure 2).

Active surveillance

If postponement of invasive treatment of locally restricted RCC (resection or ablation) is indicated or is desired by the patient, then AS is the first option. By definition, AS is indicated if any of the following apply:

- Immediate invasive therapy is currently medically contra-indicated because of temporarily elevated risks (such as recent myocardial infarction, need for multiple anticoagulant treatment, etc.) or other recent or current treatments (such as convalescence from another operation, incomplete diagnosis of another prognostically relevant disorder, etc.).
- The patient wishes, for personal or social reasons, to postpone curatively intended therapy (family or professional situation, holiday planning, etc.).
- The malignity is unclear, owing to ambiguous diagnosis, and/or the patient is afraid of side effects or complications of the treatment that might have a permanent impact upon their quality of life. In either case the patient may choose to postpone therapy and wait until there is local progression, with invasive treatment more urgently indicated (assuming that no contra-indication has arisen in the meantime). In this way the patient avoids "over-treatment".

Such decisions are reached on an individual basis, if necessary with interdisciplinary and multicentric support. Nonetheless, there remains a residual uncertainty – with both patient and physicians – as to whether the patient is after all being under-treated. There always remains a possibility that the disease will worsen during AS toward an incurable state or a more complicated treatment status – because of local disease progression, metastasis, or some other, additional disorder than might influence the patient's prognosis. This perpetual unease about the possibility of under-treatment, or excessive postponement of treatment, will in itself cause a relevant reduction in quality of life, and for this reason a large proportion of patients decide *a priori* against AS or abandon AS in favour of a definite therapy [16].

The idea of AS arose at a time when there was a lack of therapeutic alternatives to operation and, consequently, a danger of surgical over-treatment with the associated risk of substantial adverse side effects and complications, as well as increased costs for the health-care system. The theoretical basis for AS is the above-mentioned low rate of growth and metastasis for RCCs less than 3 cm in size. Strictly speaking, AS at first only comprises regular imaging for the purpose of restaging. It should only be offered for RCC with a low risk of progression and metastasis, after needle biopsy and histological confirmation of the tumour. Generally, AS is not recommended for renal tumours that are larger than 3 cm, are not sharply defined, are clearly inhomogeneous, or are found by biopsy and histology to be high-grade RCC; it is also not recommended for patients who are young and otherwise healthy. However, there is no recommended scheme setting out the type or interval of imaging. Imaging within AS should be performed at least once a year. The concept of rebiopsy within the course observation of renal tumours during AS is likewise not established. For this reason, AS is generally only conducted with check-ups by imaging. For AS of SRM and pT1a RCC there exist data from retrospective studies and metaanalyses, but there is no information from prospective, randomised studies. The increasing established possibility of ablation reduces the scope of indication for AS.

Local ablation procedures

Percutaneous ablation techniques performed under local anaesthesia are increasingly filling the gap between operative and conservative treatment. With the increasing availability of appropriate guidelines, at present more than 10% of small renal tumours are treated by ablation [1-3,34,35]. This raises a need to compare the various ablation techniques with one another, and with the various operative methods, in respect of invasiveness, quality of life, complication rate, success rate (tumour control), and post-interventional preservation of renal function. Currently there are a lack of randomised, controlled studies on this subject.

The best surgical method for preserving renal parenchyma is enucleation of the kidney tumour (Figure 3C) without ischaemia and without profound local haemostasis (the "surgical ideal"). In enucleoresection of kidney tumour (Figure 3B) and partial renal resection (Figure 3A) a variable amount of the healthy peritumoral parenchyma

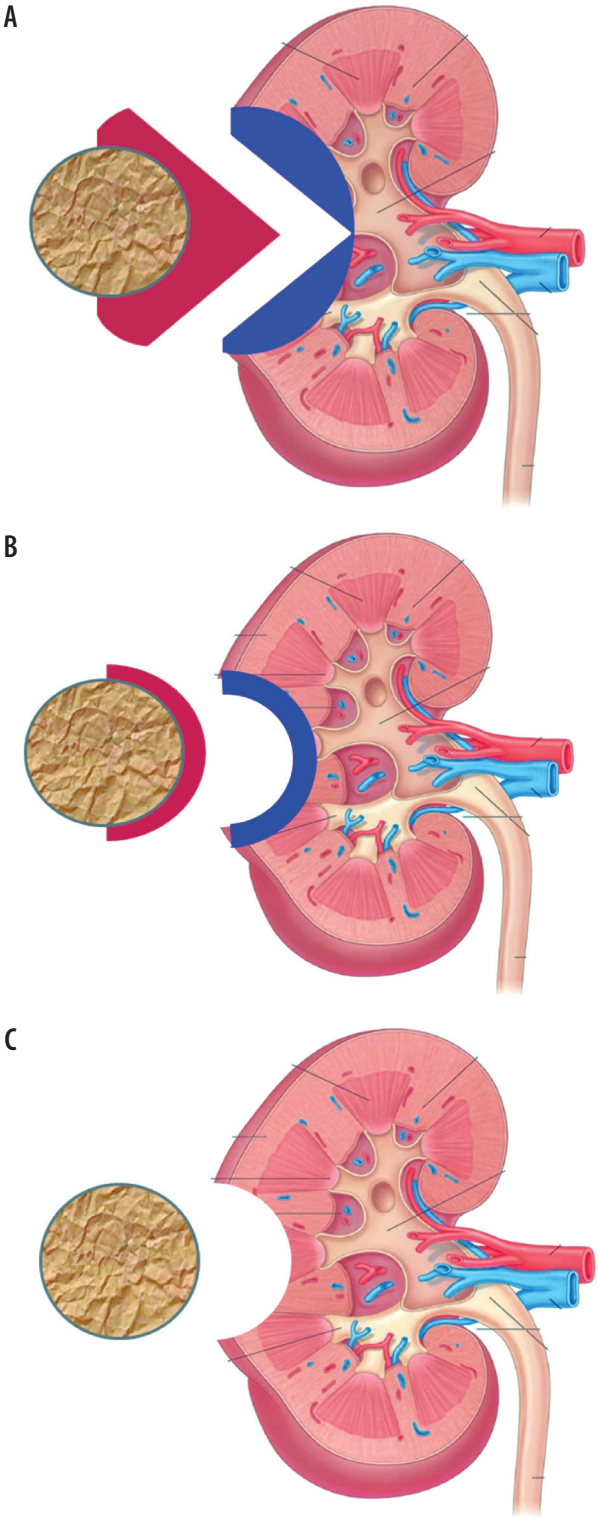

Figure 3. Operative techniques for removal of renal tumour (red, coresected healthy peritumoral parenchyma; blue, healthy parenchyma subjected to secondary damage by haemostatic and adaptive blood supply to the peripheral resected region). **A)** Partial renal resection, **B)** enucleoresection, **C)** enucleation ("ideal")

is coresected, and, as a rule, extended supply to the resection bed is performed, often with ischaemia (Figure 3). This should be contrasted with all non-surgical ablation methods; there, as a rule, the (technically inevitable) centrifugal effect gradient and the intra-interventional

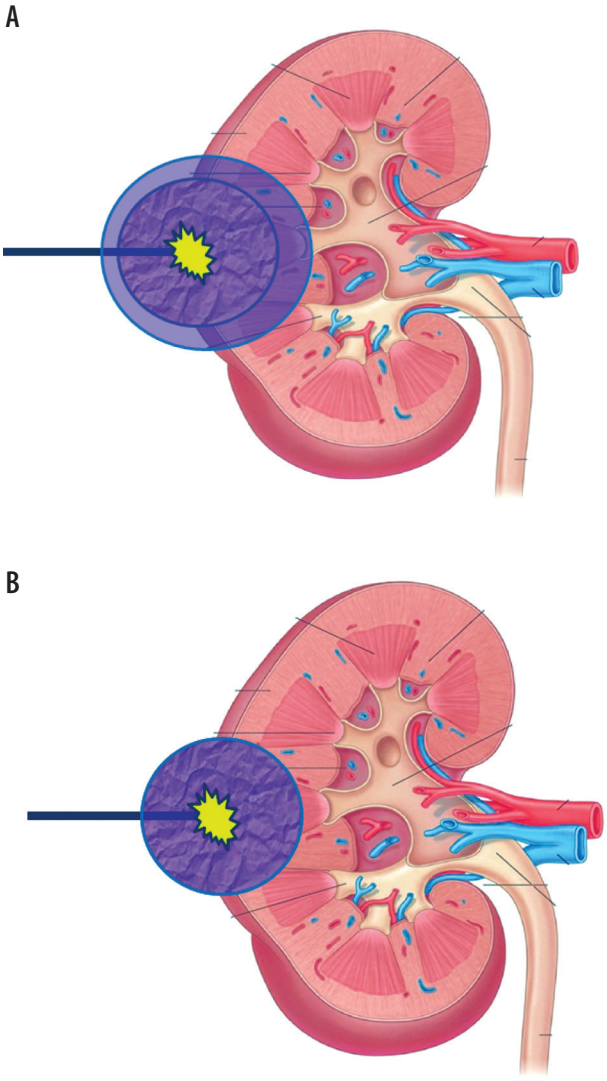

Figure 4. **A)** Renal tumour ablation with safety margin and damage to the peritumoral healthy parenchyma. **B)** Renal tumour ablation with no safety margin and no damage to the peritumoral healthy parenchyma ("ideal")

movement of the tumour and/or the organ necessitate the inclusion of a peritumoral safety margin of 5-10 mm in the healthy parenchyma (Figure 4A). More recent ablation methods, especially non-thermal ones, are aimed towards tumour ablation with a sharp demarcation of the tumour, without damage to the peritumoral parenchyma ("ablative ideal"; Figure 4B). The ablative measures are usually performed without ischaemia or embolisation. Thus, in respect of preservation of peritumoral parenchyma, the ablation is roughly comparable to renal tumour enucleoresection or enucleation, without relevant ischaemia time.

Radio-frequency ablation (RFA) and cryoablation (CA) are recommended in the guidelines of the German, European, and US-American societies for urology and radiology as alternative curative treatment options for small renal tumours in elderly patients with high morbidity, when operative or anaesthesiological risks or contra-indications are present [1-3]. Although these have been in

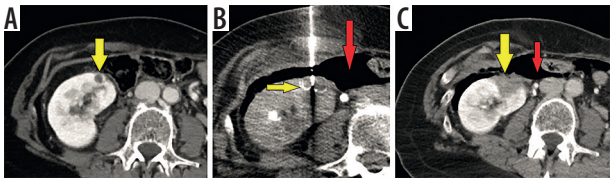

Figure 5. Radiofrequency ablation (RFA) of a renal cell carcinoma of the right kidney, **A)** pre-treatment CT scan of the right kidney with upper pole small renal mass (yellow arrow), **B)** CT scan of RFA probe (yellow arrow) with artificial pneumoperitoneum (red arrow) to displace the colon to avoid bowel necrosis/perforation, **C)** posttreatment CT scan immediately after RFA with complete necrosis of the ablation zone and tumour (yellow arrow) and the artificial pneumoperitoneum

use for some time, meaning a great deal of information is available, no results have been obtained in randomised, or even prospective, controlled studies. In a direct comparison of RFA with CA, neither procedure was found superior to the other in respect of survival (whether disease-related mortality, or progression-free or overall survival) [36]. Each has its own limitations on account of the thermoablative effect (heat-sink effect, cold-sink effect, thermal coagulative collateral damage). In the interests of more direct application and haemostasis, CA is preferentially used, by operative laparoscopy under general anaesthesia; consequently, it has no practical advantage over tumour resection, despite having the same risk of complications and being technically more complex than percutaneous RFA under local anaesthesia and analgosedation [36].

Percutaneous radio-frequency thermoablation

Percutaneous RFA is the interventional ablation method most frequently used as an alternative, non-surgical treatment of RCC. It is technically simple and relatively quick (the ablation takes 10-20 min) under fluoroscopy (CT or magnetic resonance imaging – MRI) with analgosedation. RFA is a hyperthermal ablation procedure: a high-frequency (375-480 kHz) alternating potential is applied through suitably placed needle electrodes; the resulting ion current and Joule heating to 60-100°C leads to coagulation necrosis [36]. The electrodes used are mostly expandable electrodes with multi-array tip of various sizes. A 5-10 mm safety margin is recommended for ablation. The primary success rate of RFA in SRM is between 90% and 100%, depending upon the tumour's size and position; for technical reasons, this rate is higher for corticoperipheral SRMs and those below 3 cm in size [27,37-40]. Various studies have reported local recurrence for pT1a-RCC between 2% and 12% in the first five years after RFA [38,41-45]. Moreover, RFA allows repetition, with a secondary success rate rising to nearly 100% [46]. Complications following renal RFA (0-19% of cases) are mostly mild [1,39,40,42,43,47]. Overall, RFA yields results comparable to those of partial renal resection, although no randomised studies have yet been described [1-3,43,48]. When long-term results are known, the indication may well be expanded to include RFA for treating T1a RCC. However, there is a limitation for renal tumours located centrally, directly adjacent to the hilus and the pelvicalyceal system or to large blood vessels. The strong vascularisation of RCC frequently leads, on account of the heat-sink effect (see above), to incomplete ablation [49,50]. RFA is not recommended in the vicinity of the pelvicalyceal system or the ureter on account of the risk of perforation, fistulation, or stricture [1,2,42]. These restrictions on the indication can be circumvented by alternative, non-thermal ablation methods (Figure 5).

Alternative percutaneous non-thermal ablation methods

Up to now, alternative ablation techniques have been of a largely experimental nature and have not been recommended in guidelines [1-3]. In particular, non-thermal procedures might be able to avoid thermal collateral damage and thus lead to expansion of the range of indications for RCC ablation. However, irreversible electroporation at its present stage of development is technically highly demanding and also requires intubation anaesthesia with complete muscular relaxation; therefore, it does not offer any clear advantage [51-53]. Early results of ongoing studies suggest a high potential for transcutaneous brachytherapy in the afterloading procedure and for stereotactic percutaneous radiotherapy. In particular, these radiotherapeutic procedures allow treatment without the need for anaesthesia – even in cases of large and irregularly shaped renal tumours, while taking account of respiratory movements of the kidneys.

In high-dose-rate brachytherapy (HDRBT), the target tissue is exposed to very high doses of radiation (> 12 Gy/h) by temporarily inserted radiation sources (preferentially the bemitting nuclide iridium192). After positioning of the BT catheter by Seldinger's method and analgosedation, the radiation sources are introduced for some 20-90 minutes and then removed; this follows exact, individual, three-dimensional dose planning and calculation of the duration of exposure, taking into account the target tumour volume. The characteristic fall-off in radiation intensity means that undesired high exposure of the surrounding tissue and the neighbouring organs is avoided. Currently, BT of RCC is being investigated in two ongoing prospective phase I and phase II studies in the Department of Radiology and Nuclear Medicine at Magdeburg University Hospital in Germany [36]. Preliminary results suggest good controllability and a good response of the RCC. Analogously, a high local tumour control in HDRBT, using the same techniques, has been found for adrenal-gland malignomas [54] (Figure 6).

Modern stereotactic ablative radiotherapy ("stereotactic ablative body radiotherapy" – SABR) allows precise, focussed, hypofractionated irradiation ("radiosurgery", 24-40 Gy over one to five fractions in single doses of

4-25 Gy each) in the cytotoxic region for RCC that is otherwise resistant to conventional radiotherapy. Siva *et al*. studied 223 patients treated with SABR (118 with single-fraction and 105 with multi-fraction treatments) and observed local control of 97.8% after four years, with only mild toxicity (grades 1 and 2, 35.6%; grades 3 and 4, 1.3%) [55]. Siva *et al*. reported from 33 patients with 62% T1b, 35% T1a, and 3% T2a RCC that freedom from local progression, distant progression, and overall survival rates at two years were 100%, 89%, and 92%, respectively. The mean baseline glomerular filtration rate was 55 ml/min, which decreased to 44 ml/min at one and two years ($p < 0.001$) [56]. In the German guidelines this procedure is already mentioned as a potential future treatment option [1].

Practical summary

- For patients aged over 75 years, with small RCC (< 3-4 cm), and with heightened comorbidity or advanced chronic renal insufficiency, an individual risk–benefit assessment should be performed between operative tumour resection on the one hand (as gold standard: enucleation, partial resection) and interventional ablation on the other (as an alternative treatment).
- Percutaneous biopsy, for histological confirmation and risk stratification, must be performed before ablation or AS.

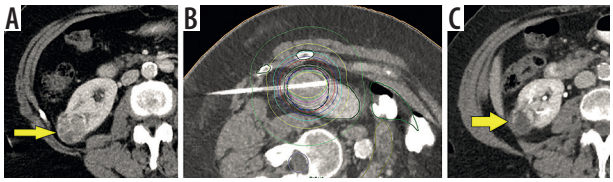

Figure 6. High-dose-rate brachytherapy (HDR-BT) of a renal cell carcinoma of the right kidney, **A)** pre-treatment CT scan of the right kidney with lower pole small renal mass (yellow arrow), **B)** CT scan of brachytherapy probe with treatment planning (isodose volume calculations) of high-dose-rate brachytherapy (afterloading), **C)** posttreatment CT scan 2 years after HDR-BT with involution of the tumour (yellow arrow)

- AS, a postponement of curative treatment with close imaging-based observation, is only to be recommended for selected patients with a low-risk RCC smaller than 3 cm.
- As an alternative, guideline-based ablation procedure for treating SRM or RCC, percutaneous thermoablative RFA without general anaesthesia has the most advantages.
- Among the ablation methods hitherto regarded as experimental, HDBRT and SABR – both non-thermal radiotherapeutic procedures – at present show the greatest potential.

Conflict of interest

The authors report no conflict of interest.

References

1. Guideline program oncology (German Cancer Society, German Cancer Aid, AWMF): Diagnostic, therapy and follow-up of the renal cell carcinoma, long version 1.2, 2017, AWMF registry number: 043/017OL. Available from: http://leitlinienprogramm-onkologie.de/Nierenzellkarzinom.85.0.html. Accessed: 16 Aug 2018.
2. European Association of Urology (2018) EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2018. ISBN 978-94-92671-01-1. Available from: http://uroweb.org/guideline/renal-cell-carcinoma/. Accessed: 16 Aug 2018.
3. American Urological Association Education and Research (2017). Renal mass and localized renal cancer: AUA guideline. Available from: http://www.auanet.org/guidelines/renal-mass-and-localized-renal-cancer-new-(2017). Accessed: 16 Aug 2018.
4. Brierley JD, Gospodarowicz MK, Wittekind C (eds.). TNM classification of malignant tumors. UICC International Union Against Cancer, 8th ed. Wiley-Blackwell, Hoboken 2017; 199.
5. Wittekind BJ, Compton CCC, Sobin LH (Hrsg). A commentary on uniform use. UICC International Union Against Cancer, 4th ed. Wiley-Blackwell, Hoboken 2013; 106.
6. Frank I, Blute ML, Cheville JC, et al. Solid renal tumors: an analysis of pathological features related to tumor size. J Urol 2003; 170: 2217-2220.
7. Wein A, Kavoussi L, Partin AW, Peters CA. Campbell-Walsh Urology. 11th ed. Elsevier, Philadelphia 2016.
8. Ziegelmüller BK, Spek A, Szabados B, et al. Epidemiology and diagnostic assessment of small renal masses. Urologe 2018; 57: 274-279.
9. Chawla SN, Crispen PL, Hanlon AL, et al. The natural history of observed enhancing renal masses: metaanalysis and review of the world literature. J Urol 2006; 175: 425-431.
10. Jewett MA, Mattar K, Basiuk J, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. Eur Urol 2011; 60: 39-44.
11. Thompson RH, Hill JR, Babayev Y, et al. Metastatic renal cell carcinoma risk according to tumor size. J Urol 2009; 182: 41-45.
12. Kim M, Choi WS, Jeong CW, et al. Differences in peritumoral pseudocapsule characteristics according to clinicopathological factors in clinical T1a renal tumors. Int J Clin Exp Pathol 2013; 8: 11323-11331.
13. Xi W, Wang J, Liu L, et al. Evaluation of tumor pseudocapsule status and its prognostic significance in renal cell carcinoma. J Urol 2018; 199: 915-920.
14. Raz O, Mendlovic S, Leibovici D, et al. The prevalence of malignancy in satellite renal lesions and its surgical implication during nephron sparing surgery. J Urol 2007; 178: 1892-1895.

15. Volpe A, Finelli A, Gill IS, et al. Rationale for percutaneous biopsy and histologic characterisation of renal tumours. Eur Urol 2012; 62: 491-504.
16. Mager R, Frees S, Haferkamp A. Watchful waiting and active surveillance of small renal masses. Urologe 2018; 57: 295-299.
17. Trpkov K, Yilmaz A, Uzer D, et al. Renal oncocytoma revisited: a clinicopathological study of 109 cases with emphasis on problematic diagnostic features. Histopathology 2010; 57: 893-906.
18. Wagener N. Renal cell carcinoma in older and geriatric patients. Urologe 2017; 56: 1019-1024.
19. Surbone A, Kagawa-Singer M, Terret C, et al. The illness trajectory of elderly cancer patients across cultures: SIOG position paper. Ann Oncol 2007; 18: 633-638.
20. Puts MT, Hardt J, Monette J, et al. Use of geriatric assessment for older adults in the oncology setting: a systematic review. J Natl Cancer Inst 2012; 104: 1133-1163.
21. Wedding U. Geriatric assessment in urology. In: Michel MS, Thüroff JW, Janetschek G, et al. The Urology. Springer, Heidelberg 2016; S2273-S2280.
22. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-383.
23. Panella L, Tinelli C, Buizza A, et al. Towards objective evaluation of balance in the elderly: validity and reliability of a measurement instrument applied to the Tinetti test. Int J Rehabil Res 2008; 31: 65-72.
24. Peyton CC, Heavner MG, Rague JT, et al. Does sarcopenia impact complications and overall survival in patients undergoing radical nephrectomy for stage III and IV kidney cancer? J Endourol 2016; 30: 229-236.
25. Abouassaly R, Yang S, Finelli A, et al. What is the best treatment strategy for incidentally detected small renal masses? A decision analysis. BJU Int 2011; 108: E223-E231.
26. Berger J, Fardoun T, Brassart E, et al. Detailed analysis of morbidity following nephrectomy for renal cell carcinoma in octogenarians. J Urol 2012; 188: 736-740.
27. Lane BR, Abouassaly R, Gao T, et al. Active treatment of localized renal tumors may not impact overall survival in patients aged 75 years or older. Cancer 2010; 116: 3119-3126.
28. Sun M, Bianchi M, Trinh QD, et al. Comparison of partial vs radical nephrectomy with regard to other-cause mortality in T1 renal cell carcinoma among patients aged ≥ 75 years with multiple comorbidities. BJU Int 2013; 111: 67-73.
29. Sun M, Becker A, Tian Z, et al. Management of localized kidney cancer: calculating cancer-specific mortality and competing risks of death for surgery and nonsurgical management. Eur Urol 2014; 65: 235-241.
30. Haferkamp A. Diagnosis and treatment of small renal masses. Urologe 2018; 57: 272-273.
31. Hellenthal NJ, Mansour AM, Hayn MH, et al. Renal cell carcinoma in octogenarians: nephron sparing surgery should remain the standard of care. J Urol 2011; 185: 415-420.
32. Pierorazio PM, Johnson MH, Patel HD, et al. Management of renal masses and localized renal cancer: systematic reviewandmeta-analysis. J Urol 2016; 196: 989-999.
33. Schmit GD, Kurup AN, Weisbrod AJ, et al. ABLATE: a renal ablation planning algorithm. AJR Am J Roentgenol 2014; 202: 894-903.
34. Moskowitz D, Chang J, Ziogas A, et al. Treatment for T1a renal cancer substratified by size: "less is more". J Urol 2016; 196: 1000-1007.
35. Kriegmair MC, Wagener N, Diehl SJ, et al. Ablative therapy of small renal masses. Urologe 2018; 57: 285-294.
36. Wendler JJ, Friebe B, Baumunk D, et al. Focal therapy for small renal masses: Observation, ablation or surgery. Urologe 2016; 55: 594-606.
37. Clark TWI, Malkowicz B, Stavropoulos SW, et al. Radiofrequency ablation of small renal cell carcinomas using multitined expandable electrodes: preliminary experience. J Vasc Interv Radiol 2006; 17: 513-519.
38. Breen DJ, Rutherford EE, Stedman B, et al. Management of renal tumors by image-guided radiofrequency ablation: experience in 105 tumors. Cardiovasc Intervent Radiol 2007; 30: 936-942.
39. Ferakis N, Bouropoulos C, Granitsas T, et al. Long term results after computed tomography-guided percutaneous radiofrequency ablation for small renal tumors. J Endourol 2010; 24: 1909-1913.
40. Zagoria RJ, Pettus JA, Rogers M, et al. Long-termoutcomes after percutaneous radiofrequency ablation for renal cell carcinoma. Urology 2011; 77: 1393-1397.
41. Kunkle DA, Uzzo RG. Cryoablation or radiofrequency ablation of the small renal mass: a meta-analysis. Cancer 2008; 113: 2671-2680.
42. Wah T, Irving H, Gregory W, et al. Radiofrequency ablation (RFA) of renal cell carcinoma (RCC): experience in 200 tumours. BJU Int 2014; 113: 416-428.
43. Olweny EO, Park SK, Tan YK, et al. Radiofrequency ablation versus partial nephrectomy in patients with solitary clinical T1a renal cell carcinoma: comparable oncologic outcomes at a minimum of 5 years of follow-up. Eur Urol 2012; 61: 1156-1161.
44. Psutka SP, Feldman AS, McDougal WS, et al. Long-term oncologic outcomes after radiofrequency ablation for T1 renal cell carcinoma. Eur Urol 2013; 63: 486-492.
45. Kroeger N, Choueiri TK, Lee JL, et al. Survival outcome and treatment response of patients with late relapse from renal cell carcinoma in the era of targeted therapy. Eur Urol 2013; 65: 1086-1092.
46. Tracy CR, Raman JD, Donnally C, et al. Durable oncologic outcomes after radiofrequency ablation: experience from treating 243 small renal masses over 7.5 years. Cancer 2010; 116: 3135-3142.
47. Varkarakis IM, Allaf ME, Inagaki T, et al. Percutaneous radio frequency ablation of renal masses: results at a 2-year mean followup. J Urol 2005; 174: 456-460.
48. Takaki H, Yamakado K, Soga N, et al. Midterm results of radiofrequency ablation versus nephrectomy for T1a renal cell carcinoma. Jpn J Radiol 2010; 28: 460-468.
49. Rendon RA, Kachura JR, Sweet JM, et al. The uncertainty of radio frequency treatment of renal cell carcinoma: findings at immediate and delayed nephrectomy. J Urol 2002; 167: 1587-1592.
50. Klingler HC, Marberger M, Mauermann J, et al. "Skipping" is still a problem with radiofrequency ablation of small renal tumours. BJU Int 2007; 99: 998-1001.
51. Wendler JJ, Pech M, Fischbach F, et al. Initial assessment of the efficacy of irreversible electroporation in the focal treatment of localized renal cell carcinoma with delayed-interval kidney tumor resection (irreversible electroporation of kidney tumors before par-

tial nephrectomy [IRENE] trial-an ablate-and-resect pilot study). Urology 2018; 114: 224-232.
52. Wendler JJ, Pech M, Köllermann J, et al. Upper-urinary-tract effects after IRreversible Electroporation (IRE) of human localised renal-cell carcinoma (RCC) in the IRENE pilot phase 2a ablate-and-resect study. Cardiovasc Intervent Radiol 2018; 41: 466-476.
53. Wendler JJ, Fischbach K, Ricke J, et al. Irreversible electroporation (IRE): standardization of terminology and reporting criteria for analysis and comparison. Pol J Radiol 2016; 81: 54-64.
54. Mohnike K, Neumann K, Hass P, et al. Radioablation of adrenal gland malignomas with interstitial high-dose-rate brachytherapy: efficacy and outcome. Strahlenther Onkol 2017; 193: 612-619.
55. Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for primaryrenal cell carcinoma: A report from the International Radiosurgery OncologyConsortium for Kidney (IROCK). Cancer 2018; 124: 934-942.
56. Siva S, Pham D, Kron T, et al. Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: a prospective clinical trial. BJU Int 2017; 120: 623-630.

Veröffentlichung 18

Radioablation of Hepatic Metastases from Renal Cell Carcinoma With Image-guided Interstitial Brachytherapy.

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Radioablation of Hepatic Metastases from Renal Cell Carcinoma With Image-guided Interstitial Brachytherapy

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Abstract. *Background/Aim: High-dose-rate interstitial brachytherapy (iBT) has been shown to provide high tumor control rates in the treatment of primary or secondary malignancies at various sites. The objective of this study was to evaluate the efficacy and safety of image-guided iBT in patients with metastatic renal cell carcinoma (mRCC). Materials and Methods: A total of 14 patients with a cumulative number of 54 unresectable RCC liver metastases after treatment with computed tomography (CT)- or open magnetic resonance imaging (MRI)-guided iBT using an iridium-192 source (single fraction irradiation) were included in this retrospective study. Results: Local tumor control rate was 92.6% during a median follow-up of 10.2 months (range=2.4-73.6 months). Median progression-free survival after iBT was 3.4 months (range=1.0-27.8 months). Median overall survival was 51.2 months (range=10.2-81.5 months). No severe adverse events (grade 3 or more) were recorded. Conclusion: Image-guided iBT is a safe and feasible treatment in patients with mRCC.*

Renal cell carcinoma (RCC) represents the sixth most common cancer in men and the tenth in woman with a rising incidence, presumably due to the more frequent incidental diagnoses of small indolent cancers (1, 2). However, locally advanced disease continues to be diagnosed in a notable proportion of patients, with up to 17-20% of all RCC being initially diagnosed with synchronous distant metastases and 40-50% of those with localized advanced disease will ultimately progress to metastatic disease (3). Without treatment the prognosis of patients with advanced or metastasized RCC (stage IV) is poor with a median survival of 6 to 12 months and a 5-year survival rate of less than 20% (4).

Due to the improved understanding of the molecular biology and genomics of RCC, the systemic treatment for metastasized RCC (mRCC) shifted over the last 15 years from a non-specific immune approach (cytokine era) to targeted therapy *e.g.* against vascular growth factor (VGEF), and to novel immunotherapy agents (*e.g.* immune-checkpoint inhibitors) (5). Impressive anti-tumor effects and prolongation of survival in patients with advanced or mRCC have been shown after treatment with these agents, for instance, VEGF tyrosine kinase inhibitor monotherapy has now been the standard first-line therapy for naïve metastatic patients, with a median overall survival of 22.9-26.4 months (6, 7). Despite their efficacy, these agents might also reduce patients' quality-of-life by causing severe adverse events (grade 3 and 4). For example, sunitinib, compared to pazopanib, causes a higher incidence of fatigue (17% *versus* 10%), hand-foot syndrome (11% *versus* 6%) and hematological toxicities (14-22% *versus* <1%) (8).

In the cytokine era, cytoreductive nephrectomy was recommended in metastatic patients with a good performance status, prior to treatment with systemic therapy. Due to the development of targeted therapies the median overall survival in patients with stage IV RCC has been extended (9, 10), hence, according to the Guidelines from the European Society for Medical Oncology (ESMO) the recommendation for nephrectomy in these patients is currently being reconsidered and only given under restricted conditions (11). Furthermore, the ESMO-guideline suggests metastasectomy and other local treatment strategies for selected patients after assessment by a multidisciplinary team (11). A recent systematic review of 16 studies including 2,350 patients sought to investigate the benefit of various local treatments of metastases from RCC (12). The results consistently suggest that patients treated

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with complete metastasectomy have better survival and symptom control than those treated with either incomplete or no metastasectomy (12). But the guideline does not state a general recommendation on whether a patient should be referred for local treatment or not.

However, in many cases surgery might not be possible due to the distribution or volume of the metastatic lesions or due to a poor performance status, apart from the surgery-associated morbidity and mortality. Aside from surgical resection, a multidisciplinary approach to localized therapy might also include image-guided local ablation techniques such as radiofrequency ablation (RFA) or interstitial brachytherapy (iBT). In iBT, an iridium-192 source is temporarily implanted into the metastatic lesions *via* percutaneously inserted applicators, which are placed under imaging guidance with a minimally invasive intervention. This technique enables a delineated single-fraction irradiation of the target volume. iBT has already been shown to be an efficient and mild treatment, with a minimum of complications, in ablation of primary or secondary malignancies at various sites (13-17). To our knowledge, no study has assessed the feasibility of iBT in the treatment of mRCC. The purpose of this retrospective study was to evaluate safety and efficacy of image-guided iBT in a cohort of patients with unresectable mRCC.

Materials and Methods

Eligibility criteria and patient population. Patient recruitment was carried out in our department between June 2006 and March 2017. A total of 14 patients (9 males and 5 females; mean age 65.1 years; range=44-78 years) with histologically proven RCC with a total of 54 liver metastases were enrolled in this retrospective analysis. All patients displayed metastatic tumor progression at the time of referral to our department and every case was discussed in an interdisciplinary tumor conference prior to iBT. Decision for iBT was taken when: (a) surgical resection was impossible or unfavorable, assessed by a surgeon with expertise in the field of visceral surgery, (b) there was contraindication for resection or severe comorbidities, (c) patient refused surgery, (d) oligometastatic disease was present (≤5 metastatic lesions, but more importantly amendable for regional treatment aimed at a complete ablation), (d) East Coast Oncology Group (ECOG) performance status below 2, (e) adequate coagulation parameters (platelet count >50,000/nl, international normalized ratio=INR>1.5, partial thromboplastin time<50 sec). No upper limit concerning the maximum tumor diameter was placed.

Prior to iBT all patients underwent nephrectomy (13/14) or partial nephrectomy (1/14). Overall, 11 out of 14 patients received first and/or second-line systemic treatment (*i.e.* 9/11 sunitinib, 2/11 sorafenib, 2/11 interleukin2, 2/11 Avastin, 3/11 Roferon, 2/11 temsirolimus, 1/11 mitomycin, 1/11 axitinib).

Three patients did not receive any systemic anticancer treatment due to reduced general condition, comorbidities or refusal of systemic treatment. A total of 5/14 patients underwent local ablation of RCC metastases prior to iBT (including local ablation using iBT or radiofrequency ablation of lung or lymph nodes metastases, or radioembolization of the liver; for detailed patient characteristics see Table I).

Table I. *Patient characteristics*.

Patient characteristics	
Total number of Patients	14
Patient gender	
Men	9
Women	5
Age at time of diagnosis (y)	
Mean	65.1
Range	44-78
Treatment of primary tumor	
Total nephrectomy	13
Partial nephrectomy	1
Distant metastases	
Metachronous	11
Synchronous	3
Patients received systemic treatment before iBT (n)	11
Sunitinib	9
Sorafenib	2
Interleukin-2	2
Avastin	2
Roferon	3
Temsirolimus	2
Mytomycin	1
Axitinib	1
localized metastatic treatment prior to iBT	
Radioembolization of the liver	3
Radiofrequency ablation of the liver	1
Radiation of mediastinal lymph node metastases	2
Total number of target lesions (n)	54
BT image guidance	
CT	29
MRT	25
Diameter of target lesion (cm)	
Median (range)	1.8 (0.5-13.9)
Number of catheters/lesions	
Median (range)	1(1-9)
Irradiation Dose BT (Gy)	
Median (range)	16.1 (6.5-27.35)
Irradiation Time BT (min)	
Median (range)	22.93 (7.0-92.32)
Local tumor control (months)	
Median (range)	10.2 (2.4-73.6)
Time to progression (months)	
Median (range)	3.4 (1.0-27.8)
Overall survival	
Median (range)	51.2 (10.2-82.5)

Patient No.4, treated in April 2016, was diagnosed with RCC of the left kidney in 1993 and a metachronous contralateral RCC in January 2014. Pre-intervention, all patients underwent a full clinical status evaluation with a physical examination and laboratory assessment. Additionally, imaging was performed using a whole-body contrast-enhanced computed tomography (CT) scan and a gadolinium (Gb)-EOB-DTPA-enhanced magnetic resonance imaging (MRI) of the liver (Primovist®, Bayer, Pharma, Leverkusen, Germany). The ethics committee of the Otto-von-Guericke-University Magdeburg approved the analysis of the patient data (Approval number: 177/18) and informed consent was obtained from all individual participants included in the study.

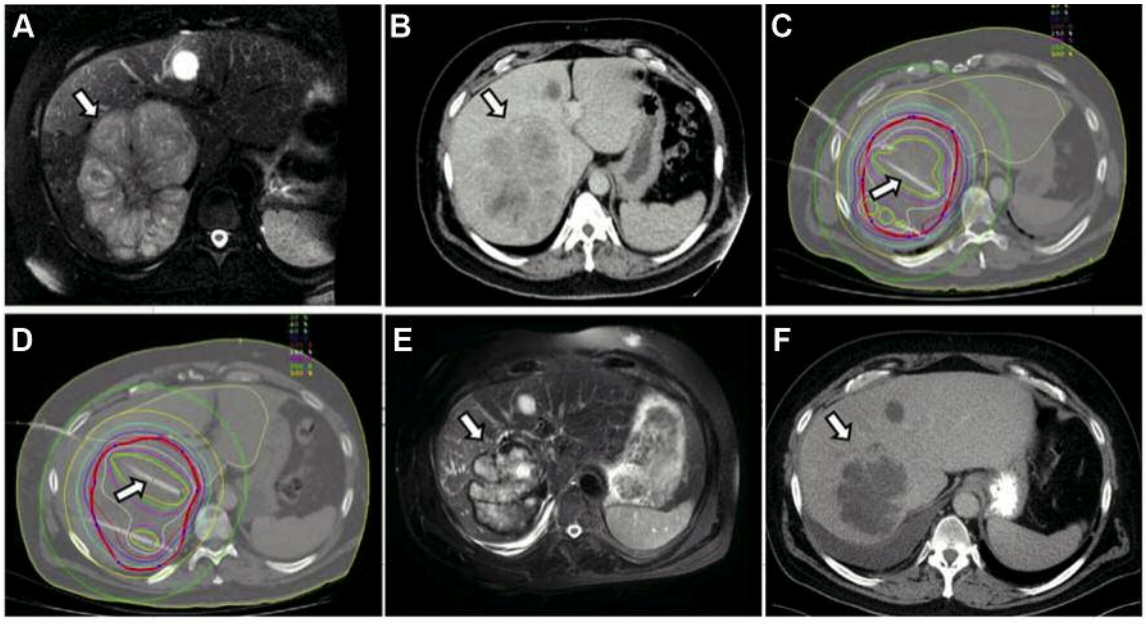

Figure 1. *Local tumor control in a patient with metastatic renal cell carcinoma in the right liver lobe. A/B: T2w MRI and pre-interventional contrast-enhanced CT: white arrow shows a metastasis from renal cell carcinoma in the left liver lobe prior to treatment by interstitial brachytherapy. C/D: Planning CT with indicated CTV (red line), catheter (marked in red) and isodose lines. E/F: Follow up MRI (E) and CT (F) after 6 months: Size reduction of the previously treated lesion in the left liver lobe (white arrow).*

Interventional technique and irradiation. iBT is an ablative radiation technique used in various inner organs, that utilizes single fraction radiation by an Iridium 192 source with a nominal activity of 10 Ci. The source is inserted into the target volume *via* percutaneously implanted catheters that are placed under image-guidance with a minimal invasive intervention under local anesthesia (lidocaine) and analgosedation (midazolam and fentanyl). The interventional technique has been described elsewhere in detail (14, 17, 18). The quantity and arrangement of the catheters used was determined by the anatomy of the target lesion.

After catheter positioning, a contrast-enhanced CT scan using a breath-holding technique or an MRI was obtained to document correct catheter positioning and to plan irradiation. Therefore, by this treatment plan the target volume was defined precisely as gross tumor volume (GTV) and as clinical target volume (CTV). Furthermore, organs at risk (OAR; *e.g.* duodenum) were delineated by the interventional radiologist and the radiooncologist.

Since the ends of the catheters were secured to the skin with a suture, the tip of the catheter was presumably in a fixed position, and CTV could be directly adopted as the planning target volume (PTV). In the next step, dose calculation was performed using the obtained dataset form Oncentra-Masterplan (Oncentra® Brachy treatment planning system, Elekta AB, Stockholm, Sweden) and the calculated isodose lines were controlled and adapted slice by slice.

The prescribed reference dose for our patients was 15 Gy and defined as the minimum dose enclosing the complete CTV (D100). Depending on OARs located in the close proximity to the CTV the D100 had to be lowered. Furthermore, in order to preserve liver function no more than 33% of the liver parenchyma was supposed to be irradiated with more than 5 Gy (19).

After irradiation, the catheters were removed and the puncture channels were sealed using thrombogenic material (*e.g.* Gelfoam®; Pfizer Inc., New York, NY, USA). Figure 1 illustrates the interventional technique.

Follow-up. All patients were scheduled for clinical, laboratory and imaging follow-ups (contrast-enhanced whole-body CT and gadolinium-enhanced MRI of the liver) every 3 months after iBT. We assessed local tumor control (LTC) and progression-free survival (PFS) by employing RECIST criteria (RECIST version1.1) on the MRI scans (20). LTC was defined as decreasing or stable presentation of the target lesion after iBT. Overall survival (OS) was calculated from the date of ablation to death. Adverse events were defined according to the 'Common Terminology Criteria for Adverse Events' (CTCAE version 4.03) (21).

Study design and statistical analysis. We retrospectively collected the data from our internally database ASENA® (LoeScap Technology GmbH). Primary endpoints were LTC and safety; secondary endpoints were OS and PFS. The results were analyzed in a non-randomized and retrospective approach and statistical analysis was performed using with IBM SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). LTC, OS and PFS were calculated using the Kaplan–Meier estimation. Safety was assessed descriptively.

Results

Mean diameter of the target lesions was 2.9 cm (range=0.7-13.9 cm). Due to their size and location, 25 lesions were

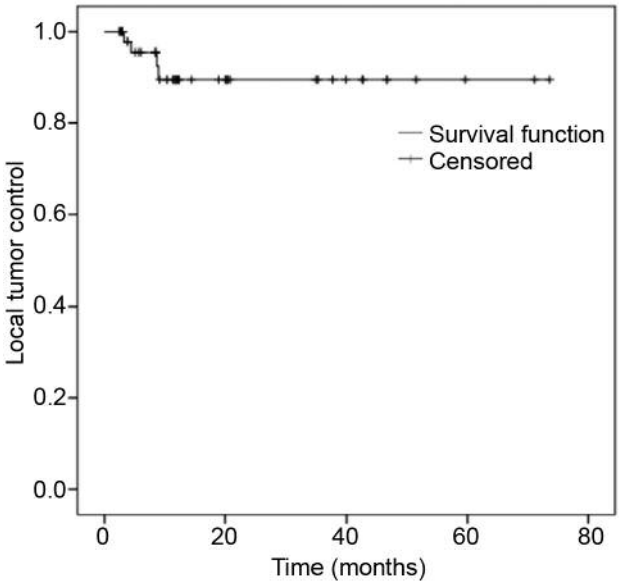

Figure 2. *Local tumor control after iBT of all treated mRCC.*

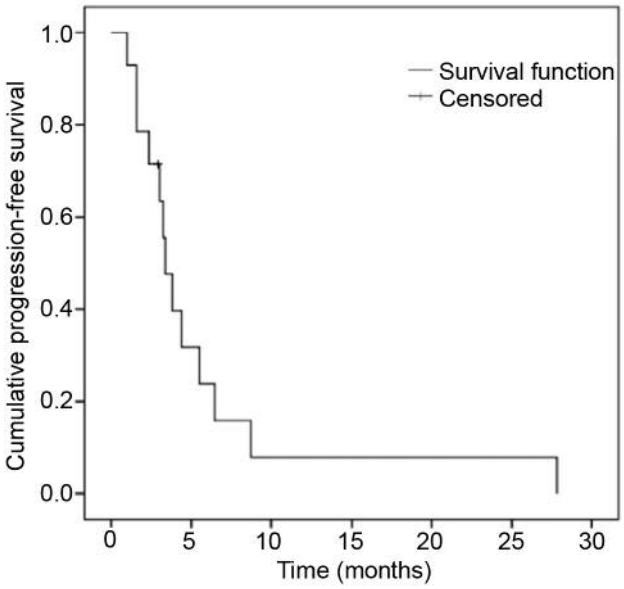

Figure 3. *Progression-free survival of patients with mRCC after iBT.*

treated using MRI scans (mean diameter=1.6 cm; range=0.5-4.8 cm), and for 29 lesions CT-guidance was used. A median of 2 lesions (range=1-12 lesions) per patient was treated, however, in each patient not more than 5 lesions were apparent and treated in one session. The high number is explained by repeated ablations in the same patient due to progressive disease. On average, the patients underwent 2.2 interventions (range=1-5); in five patients, local ablation was completed after one session, while nine patients underwent 2-5 sessions due to multiple lesions or progressive disease.

A mean of 2.0 catheters (range=1-9) was used per patient to achieve a sufficient dose application. The median administered D100 was 16.1 Gy (range=6.5-27.4 Gy). No OARs in the vicinity of the CTV were irradiated in excess of the critical value. The mean irradiation time was 27.8 min (range=7.0-92.3 min).

Hospital stay varied from 3 to 13 days with a mean of 5.3 days (median 5.0 days). We report four cases of asymptomatic hepatic hemorrhage (classified as grade 1-2 adverse event, according to CTCAE 4.03) and one asymptomatic pleural hemorrhage (grade 1); neither transfusion nor an intervention was required in these cases. In one patient, we observed increased levels of systemic inflammation markers (C-reactive protein, and leukocytosis) without fever or additional symptoms, and administration of *i.v.* antibiotics (ciproflaxacin and metronidazole) led to a rapid normalization. No severe adverse events (grade 3 or more) and no chronic or late toxicities were reported.

The median follow-up time was 10.2 months (range=2.4-73.6 months). During the follow-up period we observed 4 local recurrences in 54 treated target lesions (in a period of 3.3-8.7 months after iBT), resulting in an LTC rate of 92.6% in the Kaplan–Meier analysis (Figure 2). The mean diameter of the recurrent lesions was 2.1 cm (range=1.2-3.4 cm) covered with a median D100 of 17.0 Gy (range=15.6-19.5 Gy). Recurrence was reported in a period of 3.2-9.0 months after iBT (median 6.6 months).

Within the follow-up period 13 out of 14 patients showed systemic progressive disease, resulting in a median PFS of 3.4 months (range=1.0-27.8 months) (Figure 3).

In the period between local ablation and systemic progression, 7 patients received anticancer therapy: *i.e.* systemic treatment (2/7 sunitinib) and local ablation of newly diagnosed metastases (5/7 patients were treated with a total of 7 extrahepatic interventions: 5 BT, 2 RFA).

The median OS was 51.2 months (range=10.2-81.5 months) (Figure 4), however, at the date of censoring, 6 patients of the analyzed cohort were still alive.

In the analyzed cohort, we report that 3 patients survived for 51.5, 64.8 and 81.5 months after iBT.

Discussion

Approximately 30% of the patients with RCC display distant metastasis at initial presentation, whereas another 30% of the patients develop metastatic spread after nephrectomy, primarily to the lung, lymph nodes, bone, liver, adrenal gland, and brain (22). In general, mRCC to the liver portrays a poor prognosis, with a median OS of 7.6-12 months that is shorter, compared to the OS of patients with metastases to other sites (23, 24). For

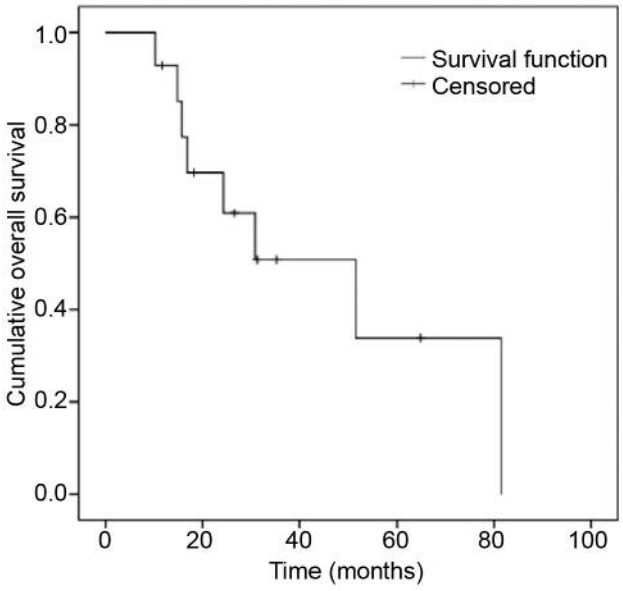

Figure 4. *Graph shows overall survival of all patients with mRCC ablated by interstitial brachytherapy.*

the patients with metastatic disease, the landscape of therapy has evolved enormously over the past two decades on the basis of an improved understanding of the molecular biology of RCC. Prior to 2005, therapy consisted mainly of immunotherapy, with agents such as interleukin-2 and interferon-a, resulting in an OS of around 1 year for patients with mRCC. With the introduction of multiple targeted therapies primarily directed at VEGF (*i.e.* axitinib, bevacizumab, pazopanib, sorafenib and sunitinib) or at the mammalian target of rapamycin (mTOR; *i.e.* everolimus and temsirolimus) the median survival improved immensely to approximately 2.5-3 years (25). Recenty, second-line treatment has been modified after a prolonged OS was shown in two randomized, phase-3 trials for cabozantinib (tyrosine kinases inhibitor=TKI) and nivolumab (programmed death-1 inhibitor): each compared to everolimus in patients with disease progression after previous VEGFR tyrosine-kinase inhibitor treatment. The results showed an improved median OS of 21.4 months *versus* 16.5 months and 25 months *versus* 19.6 months, respectively (26, 27).

However, despite impressive antitumor effects, reduction of the quality-of-life might occur due to treatment-related severe adverse events, such as diarrhea, fatigue, palmar-plantar erythrodysesthesia syndrome or anemia, for instance in the studies mentioned above grade 3 or worse adverse events occurred in 19% of the patients receiving nivolumab and in 39% of the patients treated with cabozantinib as well as in 37-40% of the patients in the everolimus group. This fact might be especially important in patients with limited tumor burden (*i.e.* oligometastatic disease) and few tumor-related symptoms.

Therapeutic alternatives for these selected patients focus on local treatment of the oligometastatic spread. However, international guidelines, like European Society for Medical Oncology (ESMO), state that no general recommendation can be given as to whether a patient should be referred for local treatment of metastases or not, but metastasectomy and other local treatment strategies, such as conventional radiotherapy or stereotactic body radiotherapy (SBRT), can be considered and carried out for selected patients after a multidisciplinary review (11). A systematic review of 16 studies reporting on 2350 patients investigated the benefits and harms of various local treatments in any organ for patients with mRCC, suggesting that patients treated with complete metastasectomy have better survival and symptom control than patients treated with no or incomplete ablation (12). Whereas surgical resection is the method of choice in oligometastatic colorectal liver metastases, evidence for surgical resection of mRCC to the liver is less available. A metanalysis of 10 studies regarding surgical management of RCC liver metastases found a median OS ranging from 16 to 142 months. Also, morbidity and mortality rates ranged from 18.2-57.1% and 0-31%, respectively, however, complications were not reported in 3/10 studies (28).

The study of Hau *et al.* was not included in the metanalysis. They reported that a group of patients who received TKI therapy immediately after metastasectomy had a median OS of 98 *versus* 40 months in the surgery-only group. However, morbidity was reported to be 28.5% with major complications occurring in 19.9% of the patients. Furthermore, microscopically complete- R0 status could be achieved in 85,7% (29). Similarly, Stief *et al.* also reported R0 status in 85% of the patients with a mean OS of 16 months after resection, high mortality rate of 31% and significant morbidity in 23% (30). Therefore, these findings of variable safety and efficacy combined with significant morbidity and mortality, as well as the limited prognosis even after R-0 resection, emphasize that this procedure strongly depends on careful patient selection.

Additionally, the latest results of a phase 3 trial (CARMENA) showed that sunitinib alone was not inferior to cytoreductive nephrectomy followed by sunitinib in patients with mRCC. More precisely, the median OS was 18.4 months in the sunitinib-alone group and 13.9 months in the nephrectomy-sunitinib group (31). According to the authors, avoiding surgery can provide benefit for the patients, in terms of avoiding surgical complications and therefore, prevent a possible delay of the start of systemic treatment, possibly accounting for the results.

Alternatively, iBT provides a safe and minimally invasive approach. As stated in the literature, grade 3-4 toxicities - *i.e.* bleeding, requiring angiographic embolization – are reported to occur in up to 2% of the patients undergoing local ablation of liver lesions (13, 14, 18, 32). In our study, we did not

observe major complications (grade 3 or worse) associated to the procedure in the post-interventional period or during the follow-up period. Accordingly, the mean hospital stay of our patients was 5.0 days, whereas, for instance, Hau *et al*. reported a median hospital stay of 18.7 days after surgery (29).

Limited data are available on the efficacy and outcome of patients with hepatic mRCC undergoing tumor ablation, including iBT, radiofrequency ablation (RFA), stereotactic body radiation (SBRT) or conventional radiotherapy. More precisely, to our knowledge, no study exists evaluating the efficacy or safety of iBT in patients with mRCC to the liver.

Similarly, data for SBRT in the treatment of hepatic metastases of RCC are scarce. However, one study analyzed 58 patients with RCC and metastases to any site, including 3 patients with liver lesions. The authors reported a LTC rate of 90.2% at 12 and 18 months, a median OS of 28.4 months and an overall low complication rate with no grade 3 or worse adverse events (33). Another investigation by Stinauer *et al*. reports a median OS of 22.2 months for 13 patients with mRCC to any organ. Also, the cumulative LTC rate was 88% since 17 patients with melanoma were also included in the study (overall 11 patients with hepatic metastases) and only one late grade 3 adverse event was observed (34).

Numerous studies have assessed the effect of RFA in the treatment of focal liver tumors; however, the method has primarily been used and evaluated for the ablation of hepatocellular carcinoma and colorectal liver metastases. For instance, Yun *et al*. treated 25 patients with non-colorectal liver metastases and no hepatocellular carcinoma (1/25 diagnosed with RCC) with a tumor size of 0.5-5 cm and found local tumor progression in 12 of 37 lesions (32%) during a median follow up period of 18.8 months (35). In the study by Langan *et al*., a group of 10 patients diagnosed with mRCC to the liver was treated with liver resection and 8 patients underwent RFA of hepatic metastases. The median OS for the surgery group was 24 months compared to 15.6 months in the RFA group (36). Mortality was nil, but morbidity was not reported for surgery and RFA separately.

Comparable to iBT, the potential benefits of RFA include reduced morbidity and mortality, low cost compared with standard surgical resection, as well as the ability to treat nonsurgical candidates. However, this thermal method has well known technical limitations; it is effective for tumor sizes <5 cm and the cooling effects arising from the vicinity of large vessels could possibly lead to an incomplete ablation. Moreover, adverse events may occur due to the proximity to heat sensitive organs (*e.g*. bile duct, ureter, liver hilum). In contrast, iBT remains free from those constraints.

In our study we report an LTC rate of 92.6% during a follow-up period of 10.2 months with no grade 3 or worse adverse events. These results are comparable to the efficacy after ablation of primary and secondary liver malignancies, demonstrating LTC rates of 95% and 88.3% after 12 months, respectively (13, 15, 19) or to the excellent LTC rate of 97.4% after the ablation of metastasized anal squamous cell carcinoma (14).

As stated above, prognosis for patients with RCC and liver metastases is poor. Consequently, the role of surgery and local therapy remains controversial. The selection of patients who might benefit from a multidisciplinary approach is essential.

In this study, we report a median OS of 51.2 months ranging from 10.2-81.5 months with three long-time survivors with OS of 51.5, 64.8 and 81.5 months, one of these patients being alive at the date of censoring. Compared to some literature reviews, the survival rates observed in our study are not inferior to those after surgery, RFA or SBRT (28, 29, 33, 34, 36). Our results emphasize that selected candidates might benefit from an ablative approach even in a metastatic setting.

Limitations of our study are its retrospective nature and the low number of patients, as well as the short follow-up that is due to the poor prognosis of the study cohort. Furthermore, the analyzed patient population was heterogeneous and comprised of patients heavily pretreated with various agents that failed to provide therapy prior to iBT and in part treated with anticancer therapy after iBT.

However, according to the literature, few data are available on local ablation of mRCC to the liver and therefore, despite its limitations, our study illustrates that iBT is an additional well-tolerated and feasible ablative technique in the toolbox for mRCC. Moreover, our findings suggest that the procedure might improve the OS of selected, oligometastatic patients.

In conclusion, our results confirm that interstitial brachytherapy is a safe and particularly effective procedure with an excellent local control rate for selected patients with metastatic renal cell cancer to the liver.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

All Authors made substantial contributions to conception and design of the study, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content. Jazan Omari and Maciej Pech approved the final version of the manuscript to be published.

References

1 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2018. CA Cancer J Clin *68(1)*: 7-30, 2018. PMID: 29313949. DOI: 10.3322/caac.21442

2 Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, Gore JL, Sun M, Wood C and Russo P: Epidemiology of renal cell carcinoma. Eur Urol *75(1)*: 74-84, 2018. PMID: 30243799. DOI: 10.1016/j.eururo.2018.08.036

3 Capitanio U and Montorsi F: Renal cancer. The Lancet *387(10021)*: 894-906, 2016. PMID: 26318520. DOI: 10.1016/S0140-6736(15)00046-X

4 Ljungberg B: The role of metastasectomy in renal cell carcinoma in the era of targeted therapy. Curr Urol Rep *14(1)*: 19-25, 2013. PMID: 23212738. DOI: 10.1007/s11934-012-0293-6

5 Lalani A-KA, McGregor BA, Albiges L, Choueiri TK, Motzer R, Powles T, Wood C and Bex A: Systemic treatment of metastatic clear cell renal cell carcinoma in 2018: Current paradigms, use of immunotherapy, and future directions. Eur Urol, 2018. PMID: 30327274. DOI: 10.1016/j.eururo.2018.10.010

6 Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM and Figlin RA: Sunitinib *versus* interferon alfa in metastatic renal-cell carcinoma. N Engl J Med *356(2)*: 115-124, 2007. PMID: 17215529. DOI: 10.1056/NEJMoa065044

7 Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, Zarbá JJ, Chen M, McCann L, Pandite L, Roychowdhury DF and Hawkins RE: Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase iii trial. J Clin Oncol *28(6)*: 1061-1068, 2010. PMID: 20100962. DOI: 10.1200/ JCO.2009.23.9764

8 Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, Staehler M, de Souza P, Merchan JR, Boleti E, Fife K, Jin J, Jones R, Uemura H, De Giorgi U, Harmenberg U, Wang J, Sternberg CN, Deen K, McCann L, Hackshaw MD, Crescenzo R, Pandite LN and Choueiri TK: Pazopanib *versus* sunitinib in metastatic renal-cell carcinoma. N Engl J Med *369(8)*: 722-731, 2013. PMID: 23964934. DOI: 10.1056/NEJMoa1303989

9 Gore ME and Larkin JM: Challenges and opportunities for converting renal cell carcinoma into a chronic disease with targeted therapies. Br J Cancer *104(3)*: 399-406, 2011. PMID: 21285971. DOI: 10.1038/sj.bjc.6606084

10 Jonasch E, Gao J and Rathmell WK: Renal cell carcinoma. BMJ *349*: g4797-g4797, 2014. PMID: 25385470. DOI: 10.1136/bmj.g4797

11 Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, Gruenvald V and Horwich A: Renal cell carcinoma: Esmo clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol *27(5)*: v58-v68, 2016. PMID: 27664262. DOI: 10.1093/annonc/mdw328

12 Dabestani S, Marconi L, Hofmann F, Stewart F, Lam TB, Canfield SE, Staehler M, Powles T, Ljungberg B and Bex A: Local treatments for metastases of renal cell carcinoma: A systematic review. Lancet Oncol *15(12)*: e549-561, 2014. PMID: 25439697. DOI: 10.1016/S1470-2045(14)70235-9

13 Collettini F, Lutter A, Schnapauff D, Hildebrandt B, Puhl G, Denecke T, Wust P and Gebauer B: Unresectable colorectal liver metastases: Percutaneous ablation using ct-guided high-dose-rate brachytherapy (ct-hdbrt). Rofo *186(6)*: 606-612, 2014. PMID: 24407711. DOI: 10.1055/s-0033-1355887

14 Heinze C, Omari J, Othmer M, Hass P, Seidensticker M, Damm R, Ricke J, Pech M and Powerski MJ: Image-guided interstitial brachytherapy in the management of metastasized anal squamous cell carcinoma. Anticancer Res *38(9)*: 5401-5407, 2018. PMID: 30194195. DOI: 10.21873/anticanres.12870

15 Mohnike K, Wieners G, Schwartz F, Seidensticker M, Pech M, Ruehl R, Wust P, Lopez-Hanninen E, Gademann G, Peters N, Berg T, Malfertheiner P and Ricke J: Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: Safety, efficacy, and effect on survival. Int J Radiat Oncol Biol Phys *78(1)*: 172-179, 2010. PMID: 20056348. DOI: 10.1016/j.ijrobp.2009.07.1700

16 Bretschneider T, Mohnike K, Hass P, Seidensticker R, Goppner D, Dudeck O, Streitparth F and Ricke J: Efficacy and safety of image-guided interstitial single fraction high-dose-rate brachytherapy in the management of metastatic malignant melanoma. J Contemp Brachytherapy *7(2)*: 154-160, 2015. PMID: 26034497. DOI: 10.5114/jcb.2015.51095

17 Ricke J and Wust P: Computed tomography-guided brachytherapy for liver cancer. Semin Radiat Oncol *21(4)*: 287-293, 2011. PMID: 21939858. DOI: 10.1016/j.semradonc.2011.05.005

18 Bretschneider T, Ricke J, Gebauer B and Streitparth F: Image-guided high-dose-rate brachytherapy of malignancies in various inner organs – technique, indications, and perspectives. J Contemp Brachytherapy *8(3)*: 251-261, 2016. PMID: 27504135. DOI: 10.5114/jcb.2016.61068

19 Ricke J, Wust P, Stohlmann A, Beck A, Cho CH, Pech M, Wieners G, Spors B, Werk M, Rosner C, Hanninen EL and Felix R: Ct-guided interstitial brachytherapy of liver malignancies alone or in combination with thermal ablation: Phase i-ii results of a novel technique. Int J Radiat Oncol Biol Phys *58(5)*: 1496-1505, 2004. PMID: 15050329. DOI: 10.1016/j.ijrobp.2003.09.024

20 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: Revised recist guideline (version 1.1). Eur J Cancer *45(2)*: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

21 Institute NC: Common terminology criteria for adverse events (ctcae) v4.03. June 14, 2010.

22 Motzer RJ, Jonasch E, Agarwal N, Bhayani S, Bro WP, Chang SS, Choueiri TK, Costello BA, Derweesh IH, Fishman M, Gallagher TH, Gore JL, Hancock SL, Harrison MR, Kim W, Kyriakopoulos C, LaGrange C, Lam ET, Lau C, Michaelson MD, Olencki T, Pierorazio PM, Plimack ER, Redman BG, Shuch B, Somer B, Sonpavde G, Sosman J, Dwyer M and Kumar R: Kidney cancer, version 2.2017, nccn clinical practice guidelines in oncology. J Natl Compr Canc Netw *15(6)*: 804-834, 2017. PMID: 28596261. DOI: 10.6004/jnccn.2017.0100

23 Hamada S, Ito K, Kuroda K, Sato A, Asakuma J, Horiguchi A, Seguchi K and Asano T: Clinical characteristics and prognosis of patients with renal cell carcinoma and liver metastasis. Mol Clin Oncol *3(1)*: 63-68, 2015. PMID: 25469271. DOI: 10.3892/mco.2014.432

24 Naito S, Yamamoto N, Takayama T, Muramoto M, Shinohara N, Nishiyama K, Takahashi A, Maruyama R, Saika T, Hoshi S, Nagao K, Yamamoto S, Sugimura I, Uemura H, Koga S, Takahashi M, Ito F, Ozono S, Terachi T, Naito S and Tomita Y: Prognosis of japanese metastatic renal cell carcinoma patients in the cytokine era: A cooperative group report of 1463 patients. Eur Urol *57(2)*: 317-326, 2010. PMID: 19136199. DOI: 10.1016/j.eururo.2008.12.026

25 Pal SK, Choueiri TK, Karam JA and Heng DY: Metastatic renal cell carcinoma: Contending with a sea change in therapy. Urol Oncol *33(12)*: 507-508, 2015. PMID: 26584741. DOI: 10.1016/j.urolonc.2015.10.005

26 Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, Hammers HJ, Donskov F, Roth BJ, Peltola K, Lee

JL, Heng DYC, Schmidinger M, Agarwal N, Sternberg CN, McDermott DF, Aftab DT, Hessel C, Scheffold C, Schwab G, Hutson TE, Pal S and Motzer RJ: Cabozantinib *versus* everolimus in advanced renal cell carcinoma (meteor): Final results from a randomised, open-label, phase 3 trial. Lancet Oncol *17(7)*: 917-927, 2016. PMID: 27279544. DOI: 10.1016/S1470-2045(16)30107-3

27 Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM and Sharma P: Nivolumab *versus* everolimus in advanced renal-cell carcinoma. N Engl J Med *373(19)*: 1803-1813, 2015. PMID: 26406148. DOI: 10.1056/NEJMoa1510665

28 Pikoulis E, Margonis GA and Antoniou E: Surgical management of renal cell cancer liver metastases. Scand J Surg *105(4)*: 263-268, 2016. PMID: 26929295. DOI: 10.1177/1457496916630644

29 Hau HM, Thalmann F, Lübbert C, Morgul MH, Schmelzle M, Atanasov G, Benzing C, Lange U, Ascherl R, Ganzer R, Uhlmann D, Tautenhahn H-M, Wiltberger G and Bartels M: The value of hepatic resection in metastasic renal cancer in the era of tyrosinkinase inhibitor therapy. BMC Surg *16(1)*: 49-49, 2016. PMID: 27444582. DOI: 10.1186/s12893-016-0163-0

30 Stief CG, Jahne J, Hagemann JH, Kuczyk M and Jonas U: Surgery for metachronous solitary liver metastases of renal cell carcinoma. J Urol *158(2)*: 375-377, 1997. PMID: 9224306.

31 Méjean A, Ravaud A, Thezenas S, Colas S, Beauval J-B, Bensalah K, Geoffrois L, Thiery-Vuillemin A, Cormier L, Lang H, Guy L, Gravis G, Rolland F, Linassier C, Lechevallier E, Beisland C, Aitchison M, Oudard S, Patard JJ, Theodore C, Chevreau C, Laguerre B, Hubert J, Gross-Goupil M, Bernhard JC, Albiges L, Timsit MO, Lebret T and Escudier B: Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med *379(5)*: 417-427, 2018. PMID: 29860937. DOI: 10.1056/NEJMoa1803675

32 Geisel D, Denecke T, Collettini F, Grieser C, Wust P, Thuss-Patience P, Hamm B and Gebauer B: Treatment of hepatic metastases from gastric or gastroesophageal adenocarcinoma with computed tomography-guided high-dose-rate brachytherapy (ct-hdrbt). Anticancer Res *32(12)*: 5453-5458, 2012. PMID: 23225451.

33 Franzese C, Franceschini D, Di Brina L, D'Agostino Giuseppe R, Navarria P, Comito T, Mancosu P, Tomatis S and Scorsetti M: Role of stereotactic body radiation therapy for the management of oligometastatic renal cell carcinoma. J Urol *201(1)*: 70-76, 2019. PMID: 30179619. DOI: 10.1016/j.juro.2018.08.049

34 Stinauer MA, Kavanagh BD, Schefter TE, Gonzalez R, Flaig T, Lewis K, Robinson W, Chidel M, Glode M and Raben D: Stereotactic body radiation therapy for melanoma and renal cell carcinoma: Impact of single fraction equivalent dose on local control. Radiation Oncology *6(1)*: 34, 2011. PMID: 21477295. DOI: 10.1186/1748-717X-6-34

35 Yun BL, Lee JM, Baek JH, Kim SH, Lee JY, Han JK and Choi BI: Radiofrequency ablation for treating liver metastases from a non-colorectal origin. Korean J Radiol *12(5)*: 579-587, 2011. PMID: 21927559. DOI: 10.3348/kjr.2011.12.5.579

36 Langan RC, Ripley RT, Davis JL, Prieto PA, Datrice N, Steinberg SM, Bratslavsky G, Rudloff U, Kammula US, Stojadinovic A and Avital I: Liver directed therapy for renal cell carcinoma. J Cancer *3*: 184-190, 2012. PMID: 22558019. DOI: 10.7150/jca.4456

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First report on extended distance between tumor lesion and adjacent organs at risk using interventionally applied balloon catheters: a simple procedure to optimize clinical target volume covering effective isodose in interstitial high-dose-rate brachytherapy of liver malignomas.

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Original paper

First report on extended distance between tumor lesion and adjacent organs at risk using interventionally applied balloon catheters: a simple procedure to optimize clinical target volume covering effective isodose in interstitial high-dose-rate brachytherapy of liver malignomas

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Abstract

Purpose: Organs at risk (OARs), which are very close to a clinical target volume (CTV), can compromise effective tumor irradiation. The present study investigated the feasibility and safety of a novel approach, in particular, the extent of the dosimetric effect of distancing CTV from adjacent OARs by means of interventionally applied balloon catheters.

Material and methods: Patients with peripheral hepatic malignancies, in whom the critical proximity of an OAR to the CTV in the assessment by contrast-enhanced magnetic resonance imaging (MRI) scans and the preplanning process were included. Additionally, patients underwent placement of an interventional balloon catheter during computed tomography (CT)-guided application of interstitial brachytherapy (iBT) catheters inserted into the tissue between hepatic capsule and adjacent OAR. The virtual position of an OAR without balloon catheter was anticipated and contoured in addition to contouring of CTV and OAR. The calculated dose values for CTV as well as 1 cc of the relevant OAR (D_{1cc}) with and without balloon were recorded. The D_{1cc} of the realized irradiation plan was statistically compared to the D_{1cc} of the virtually contoured OARs.

Results: In 31 cases, at least one balloon catheter was administered. The mean D_{1cc} of the OAR in the group with balloon(s) was 12.6 Gy compared with 16 Gy in the virtual cohort without the device, therefore significantly lower ($p < 0.001$). Overall, there were no acute complications. Severe (> 2 CTCAEv4.03) late complications observed in 3/31 (9.6%) patients during follow-up period after brachytherapy were most certainly not due to the balloon application. Side effects were probably associated with pre-existing serious diseases and potentially additional local late effects of the irradiation in general rather than with the balloon catheters.

Conclusions: The distancing of the adjacent OARs allows a higher D_{100} value of CTV, therefore allowing for more efficient local control.

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Key words: balloon catheters, clinical target volume (CTV), dose per 1 cc (D_{1cc}), dose volume histogram (DVH), interstitial high-dose-rate (HDR) brachytherapy (iBT), liver malignancies, organ at risk (OAR).

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Purpose

The concept of oligo-metastasis [1] based on surgical studies [2,3,4] that was discussed for the first time in the 1990s, differs from the rigid scheme of palliation vs. curation. There is a cohort of oligo-metastasized patients, which is not yet clearly definable that benefits from a consequent local ablation in terms of an improvement in the overall prognosis [5]. The gold standard of local treatment is surgical procedure [6]. However, since a high proportion of hepatic oligo-metastases is not resectable, alternative ablation procedures have been successfully tested [7]. The "toolbox of ablative treatments" is now a part of the current "ESMO (European Society for Medical Oncology) guidelines for the management of patients with metastatic colorectal cancer" [8].

In this study, radio-ablative methods are particularly investigated.

The development of high-performance software for calculation and application of prescribed irradiation dose and device-based hardware, currently allow for very precise implementation of hypo-fractionated and radio-surgical approaches [9,10]. Therefore, in no resectable patient, primary and secondary liver malignancies can often be treated very effectively with radiotherapy [11]. The key for effective and sustainable radio-ablation is to provide adequate clinical target volume doses [12,13], taking into account the dose limits of adjacent organs at risk (OARs). Particularly, in the case of marginal liver tumor, compromises cannot often be avoided at the expense of a potentially reduced chance of local control.

The aim of the present analysis was to investigate the feasibility and safety of a novel approach, in particular, to examine whether an increase in the distance between the target volume and the structure at risk is technically possible without severe complications and to what extent a dosimetric advantage is generated.

Material and methods

Patients

As a rule, all patients who might be eligible for brachytherapy of the liver are considered by a tumor board prior to the initial presentation at our department. A standard operating procedure (SOP) defines the inclusion and exclusion criteria for performing interstitial brachytherapy (iBT) of the liver. All patients sign a written informed consent prior to planning a computed tomography (CT)- or magnet resonance imaging (MRI)-guided interstitial brachytherapy. From April 2009 to June 2016, 2,082 patients with primary or secondary liver tumors were treated with interstitial high-dose-rate (HDR) brachytherapy; 137 cases (6.6%) had subcapsular liver tumors near the stomach, duodenum, or large intestine (OAR).

From this cohort, 31 patients were included in the study and received one or two additional balloon catheter(s) to increase the distance between the hepatic margin/surface and adjacent OAR, as part of single stage CT-guided iBT (recorded dose-volume histogram (DVH) parameters, Table 1 and Figure 1).

The prescribed dose related to D_{100} depends on the histology of the primary tumor lesion (GIST [gastrointestinal stromal tumor] = 12 Gy, breast cancer, renal cell carcinoma, hepatocellular carcinoma = 15 Gy, other histologies = 20 Gy). The dose was applied as a single fraction targeted on the complete tumor ablation.

Method

Methodology and course of single-dose interstitial HDR brachytherapy was already described in detail elsewhere [12,14].

Briefly, HDR-brachytherapy catheters (Primed, Halberstadt, Germany) and angiographic occlusion balloon catheters (Equalizer™ Occlusion Balloon Catheter, 20 and 27 mm, Boston Scientific, Marlborough, USA) were placed in a similar way using CT fluoroscopy (Aquilion Prime, Canon Medical Systems, Neuss, Germany). Following the puncture of the target lesion (for brachytherapy catheters) or between the liver capsule with the adjacent target lesion and the OAR (for balloon catheters) with an 18-G coaxial needle, a stiff angiography wire (Amplatz Super Stiff™, Boston Scientific, Boston, MA, USA) was introduced for placement of a 6 F (for brachytherapy catheters) or 12 F (for balloon catheters) introducer sheath (Radifocus®, Terumo, Tokyo, Japan), using the Seldinger technique, through which the brachytherapy or balloon catheter was inserted. When in the correct position, the balloon catheter was inflated (with contrast medium) to dissociate the OAR from the target volume (Figure 2). After placement of brachytherapy and balloon catheters, a contrast agent-enhanced (intravenously, iodine-based, 80 ml) spiral CT in breath-holding-technique (slice thickness, 3 mm) of the liver was acquired. The catheter position, the tumor margin, and anatomic risk structures verified by contrast-enhanced images were sent to the treatment planning unit (Oncentra Brachy, Elekta AB, Stockholm, Sweden).

The decision to insert a balloon catheter was made after the evaluation of liver specific MRI scans (slice thickness, 3 mm; MRI protocol included: T2-weighted ultra-turbo spin echo sequences with and without fat saturation, diffusion-weighted imaging, a T1-weighted gradient echo sequence, T1-weighted dynamic sequences, and sequences acquired 20 min after IV administration of 0.1 ml/kg Gd-EOB-DTPA [Primovist®, Bayer Vital, Leverkusen, Germany] performed on an 1.5-tesla MRI scanner [Intera 1.5T, Philips Healthcare, Hamburg, Germany], if within the framework of a virtual catheter application, the calculated clinical target volume (CTV) enclosing prescription dose (D_{100}) did not seem to be feasible under consideration of the institutional OAR dose limits concerning D_{1cc} and V_5 [13,15,16], and outstanding publications and reviews, inter alia, by Timmermann, Herfarth *et al*. and Sterzing *et al*. [17,18,19] (Table 2).

The time for insertion of one balloon catheter corresponds approximately to the application time of two BT catheters (mean, 16 min). In case of an implant with one BT catheter tripling the intervention time and in case of more advanced liver lesions with 8 catheters, the duration time of the intervention increases by approximately 25%.

Table 1. Recorded dose-volume histogram (DVH) parameters

Patient study number	Prescribed single-dose for D_{100} CTV (Gy)	Calculated dose for D_{100} CTV with balloon (Gy)	Adjacent OAR	Accepted calculated dose for OAR $D1_{cc}$ with balloon (Gy)	Calculated dose for anticipated OAR without balloon
1	20	10.560	Stomach	15.720	16.195
2	12	6.700	Stomach	13.500	21.798
3	15	7.740	Duodenum	12.250	12.420
4	20	8.750	Stomach	14.250	15.610
5	20	9.330	Stomach	13.938	16.501
6	15	15.117	Large intestine	16.540	25.130
7	20	11.010	Stomach	13.880	14.440
8	15	14.250	Stomach	12.980	15.460
9	20	20.300	Stomach	9.320	13.924
10	15	12.050	Stomach	14.010	15.456
11	20	20.580	Duodenum	13.510	16.160
12	20	20.930	Stomach	14.220	15.625
13	20	20.670	Stomach	11.390	14.310
14	20	20.830	Stomach	13.560	14.290
15	20	15.886	Stomach	14.350	15.964
16	15	15.130	Stomach	8.970	21.030
17	12	12.310	Stomach	11.290	13.390
18	15	15.240	Stomach	14.280	23.787
19	15	13.140	Stomach	11.160	13.910
20	20	20.827	Stomach	9.200	11.130
21	20	15.440	Stomach	12.310	14.700
22	15	9.940	Stomach	13.685	14.957
23	15	15.146	Stomach	10.230	13.389
24	25	27.420	Stomach	9.920	16.870
25	25	25.300	Stomach	13.430	17.220
26	20	15.150	Stomach	14.810	14.920
27	25	25.290	Stomach	13.640	17.688
28	20	20.700	Stomach	12.220	15.497
29	25	27.560	Stomach	8.890	18.160
30	15	13.900	Stomach	10.437	11.300
31	20	22.530	Stomach	13.710	15.459

Prescribed and calculated dose for D_{100}-CTV, accepted calculated dose for OAR-D_{1cc} with balloon, calculated dose for OAR-D_{1cc} regarding anticipated OAR-contour without balloon.

In addition to CTV, liver and adjacent OAR (predominantly stomach) as well as virtual OAR volume without a balloon were contoured; the virtual position of the OAR could be anticipated by assessing the pre-interventional MRI scans and additionally, with the interventional CT scans with BT catheter only (Figure 1).

Dose calculation was performed in strict accordance with institutional OAR limits (Table 2). The relevant parameters for this analysis such as prescription dose, D_{100}-CTV, D_{1cc}-OAR with and without a balloon were recorded. The values for the $D1_{cc}$-OAR with and $D1_{cc}$-OAR without balloon were distinguished as two groups and statistically evaluated.

The values for $D1_{cc}$-OAR with and $D1_{cc}$-OAR without balloon were assigned to two groups. These two cohorts were compared statistically.

Interstitial HDR brachytherapy was performed using an ^{192}Ir source with an afterloading device from Elekta (MicroSelectron HDR V3, Oncentra Brachy, Elekta AB, Stockholm, Sweden).

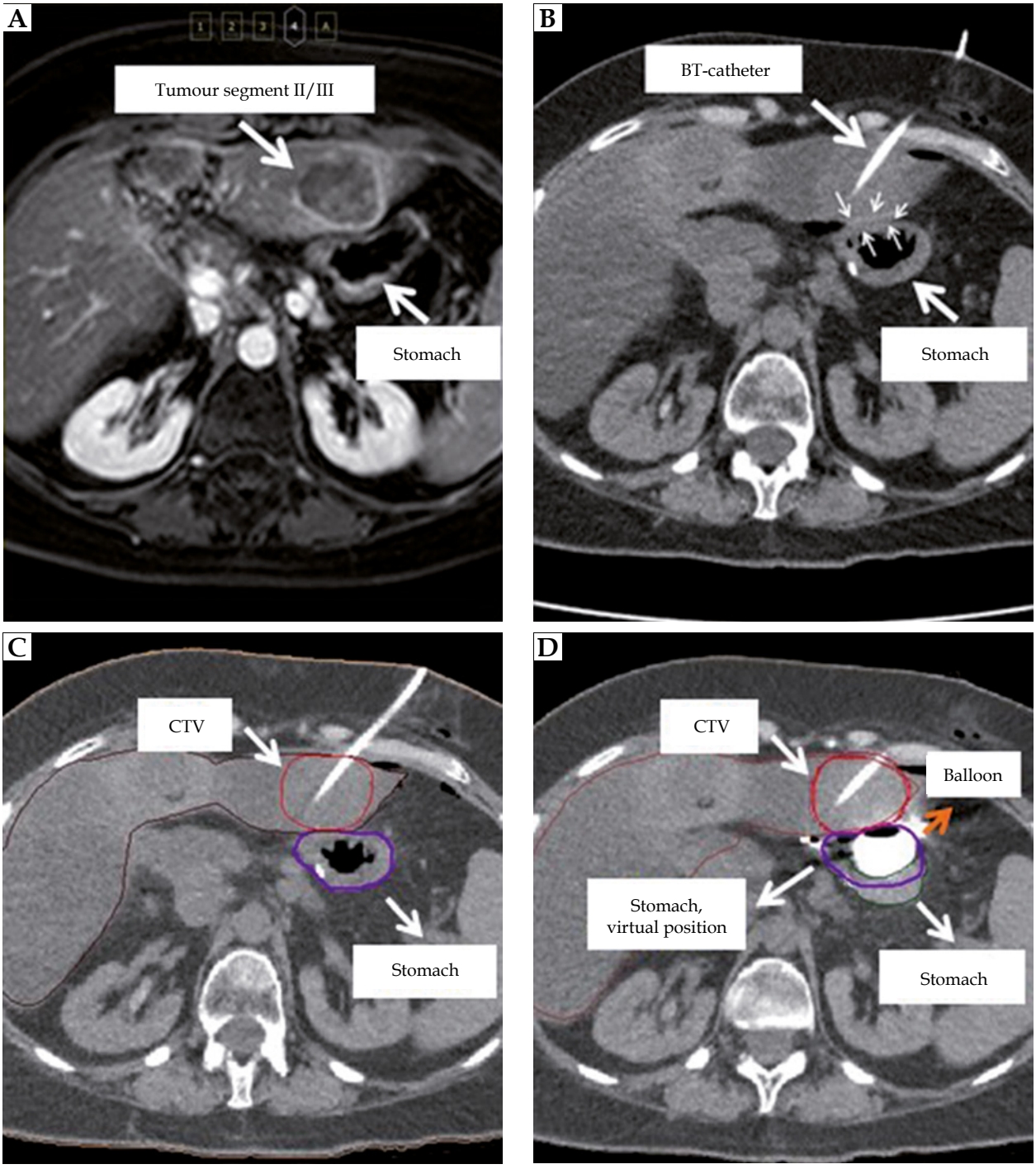
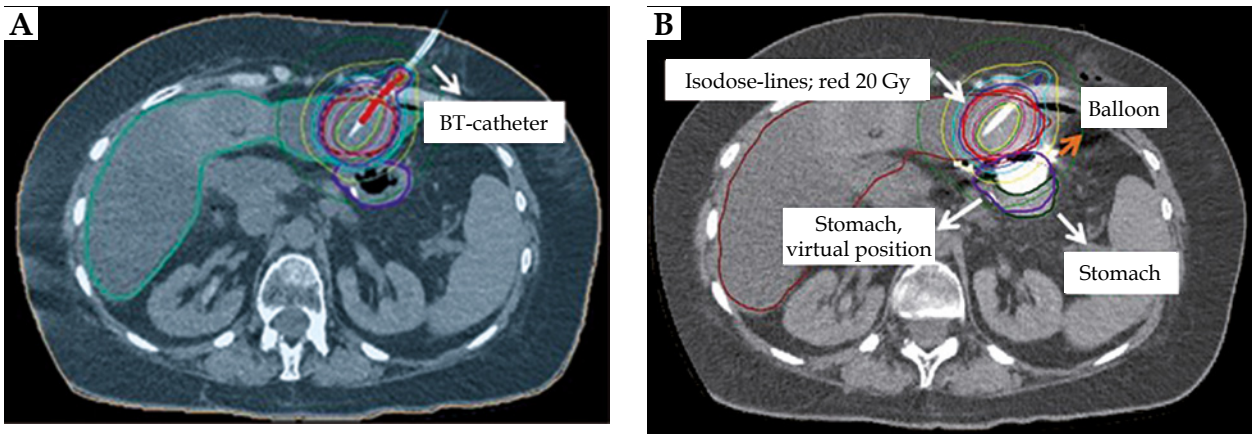


Fig. 1. Tomography imaging: **A**) Transversal MRI-scan: tumor lesion with marginal enhancement of contrast media, no BT, catheter; distinctly adjacent stomach; **B**) Corresponding transversal CT-scan with stomach position without balloon; one BT, catheter inserted; **C**) Corresponding transversal CT-scan; CTV and stomach contoured; **D**) Corresponding transversal CT-scan with additional balloon; CTV, stomach and stomach, virtual position without balloon contoured

Statistics

Statistics were collected with R (version 3.1.3; the R Foundation for Statistical Computing, Vienna, Austria).

Due to small sample size, non-parametric distribution of data was assumed, and data were described by median, interquartile range (IQR, 25^{th}-75^{th} percentiles), and minimum and maximum. Boxplots were used for visualization of data. Correlation of data was analyzed with Spearman's rho rank correlation coefficient and agreement of methods was described using Bland-Altman analysis [20]. Paired groups (with/without balloon) were compared with Wilcoxon signed rank test, and optimal cut-off was determined using receiver operating characteristics (ROC) curves [21] and Youden index as appro-



Resulting $D1_{cc}$	Dose (%)	Dose (Gy)	Volume (%)	Volume (ccm)
Stomach without balloon	113.09	22.6184	0.10	0.10
Liver without balloon	–	–	0.01	0.10
Stomach with balloon	89.84	17.9685	0.10	0.10
Liver with balloon	–	–	0.01	0.10
Stomach without balloon	86.23	17.2459	0.97	1.00
Liver without balloon	–	–	0.06	1.00
Stomach with balloon	69.65	13.9301	1.01	1.00
Liver with balloon	–	–	0.06	1.00

Fig. 2. Planning transversal CT scan with isodoses, prescribed dose to D_{100} CTV 20 Gy: **A**) CT-scan without balloon, one BT-catheter inserted; **B**) CT-scan with BT-catheter and one balloon-catheter inserted

priate. All tests were two-sided, and the significance level was set as 0.05.

Statement

The study was performed according to the guidelines of the Declaration of Helsinki for Biomedical Research from 1964 and its further amendments, and the procedures of "Good Research Practice". The analysis was designed as a retrospective study with approval of the local ethics committee. Each patient signed a written consent form prior to the planned intervention after an adequate patient-physician talk on the intervention and the frequency, severity, and profile of its complications.

Results

Patients

Thirty-one patients (17 females, 14 males; median age, 65.3 [range, 38-85] years), 22% of those with subcapsular liver tumors, were enrolled in the study. In 25 cases, one in 6 cases, two balloon catheters were inserted.

In 74% of the patients, primary lesions outside the liver were histologically confirmed (colorectal carcinoma, 45%; others, 29%), 26% had primary liver malignancies.

The marginal hepatic lesions were located within the liver segments 2/3 in 29 cases (93.5%), 2 patients had lesions within the right hepatic lobe, near large

Table 2. Dose constraints regarding organs at risk for single dose

Organ at risk	Timmermann SBRT constraints [17]		Herfarth, Sterzing, SBRT constraints [18,19]		Institutional constraints due to prospective and retrospective analysis of the XX/YY study-group [13,15,16]	
	DVH-parameter	Limit (Gy)	DVH parameter	Limit (Gy)	DVH parameter	Limit (Gy)/(%)
Stomach	D_{10cc}	< 13.0	D_{max}	12.0	D_{1cc}	14 (15*)
Duodenum	D_{5cc}	< 8.8	D_{max}	12.0	D_{1cc}	14 (15*)
Colon	D_{20cc}	< 11.0	Not specified	Not specified	D_{1cc}	18
Liver	D_{700cc}	9.1	D_{50}	4.0-7.0	V_5	/66

**The original values based on Streitparth's work [13] were decreased to 14 Gy from 2012 to further reduce the risk of late toxicity.*

Table 3. Patients' characteristics

Patient study number	Age (yr) at time of treatment	Gender	OAR	Primary tumor diagnosis	CTV volume (ccm)	Number (*n*) of balloon catheters
1	78	Male	Stomach	Colorectal cancer	23.75	1
2	68	Male	Stomach	Gastrointestinal stromal tumor	3.34	1
3	44	Female	Duodenum	Leiomyosarcoma	3.74	1
4	67	Male	Stomach	Colorectal cancer	191.7	2
5	57	Female	Stomach	Colorectal cancer	143.3	1
6	63	Male	Large intestine	Renal cell cancer	22.3	1
7	54	Female	Stomach	Colorectal cancer	87.95	2
8	64	Female	Stomach	Cholangiocellular carcinoma	336.0	2
9	69	Male	Stomach	Cholangiocellular carcinoma	10.3	1
10	77	Male	Stomach	Hepatocellular cancer	10.36	1
11	70	Male	Duodenum	Cholangiocellular carcinoma	62.7	1
12	74	Female	Stomach	Colorectal cancer	40.68	2
13	69	Female	Stomach	Colorectal cancer	18.75	1
14	48	Female	Stomach	Pancreatic cancer	31.48	1
15	56	Female	Stomach	Colorectal cancer	134.0	2
16	38	Female	Stomach	Breast cancer	3.54	1
17	73	Male	Stomach	Gastrointestinal stromal tumor	32.35	1
18	74	Male	Stomach	Cancer of unknown primary	9.37	1
19	46	Female	Stomach	Breast cancer	43.76	1
20	71	Female	Stomach	Colorectal cancer	28.81	1
21	75	Female	Stomach	Colorectal cancer	101.6	1
22	80	Male	Stomach	Colorectal cancer	135.2	1
23	84	Female	Stomach	Hepatocellular cancer	1.7	1
24	56	Female	Stomach	Cholangiocellular carcinoma	2.96	1
25	60	Male	Stomach	Colorectal Cancer	50.54	1
26	85	Male	Stomach	Colorectal Cancer	74.0	1
27	47	Male	Stomach	Colorectal cancer	9.3	1
28	74	Female	Stomach	Gallbladder cancer	3.1	1
29	70	Female	Stomach	Cancer of unknown primary	35.53	2
30	62	Male	Stomach	Hepatocellular cancer	12.3	1
31	71	Female	Stomach	Colorectal cancer	35.42	1

intestine. Patients' characteristics are presented in Table 3.

Application time for the whole implant depended on the number of inserted BT catheters and additional balloons. Median application time was 12.5 min (range, 7.5-30 min).

Organs at risk (stomach/duodenum, large intestine) D_{1cc}

D_{1cc} of the OAR with balloon (mean, 12 Gy; deviation, 8.9 to 16.5 Gy; median, 13.5 Gy; IQR, 11.2 to 14.0 Gy) were significantly ($p < 0.001$) lower compared to virtual antic-

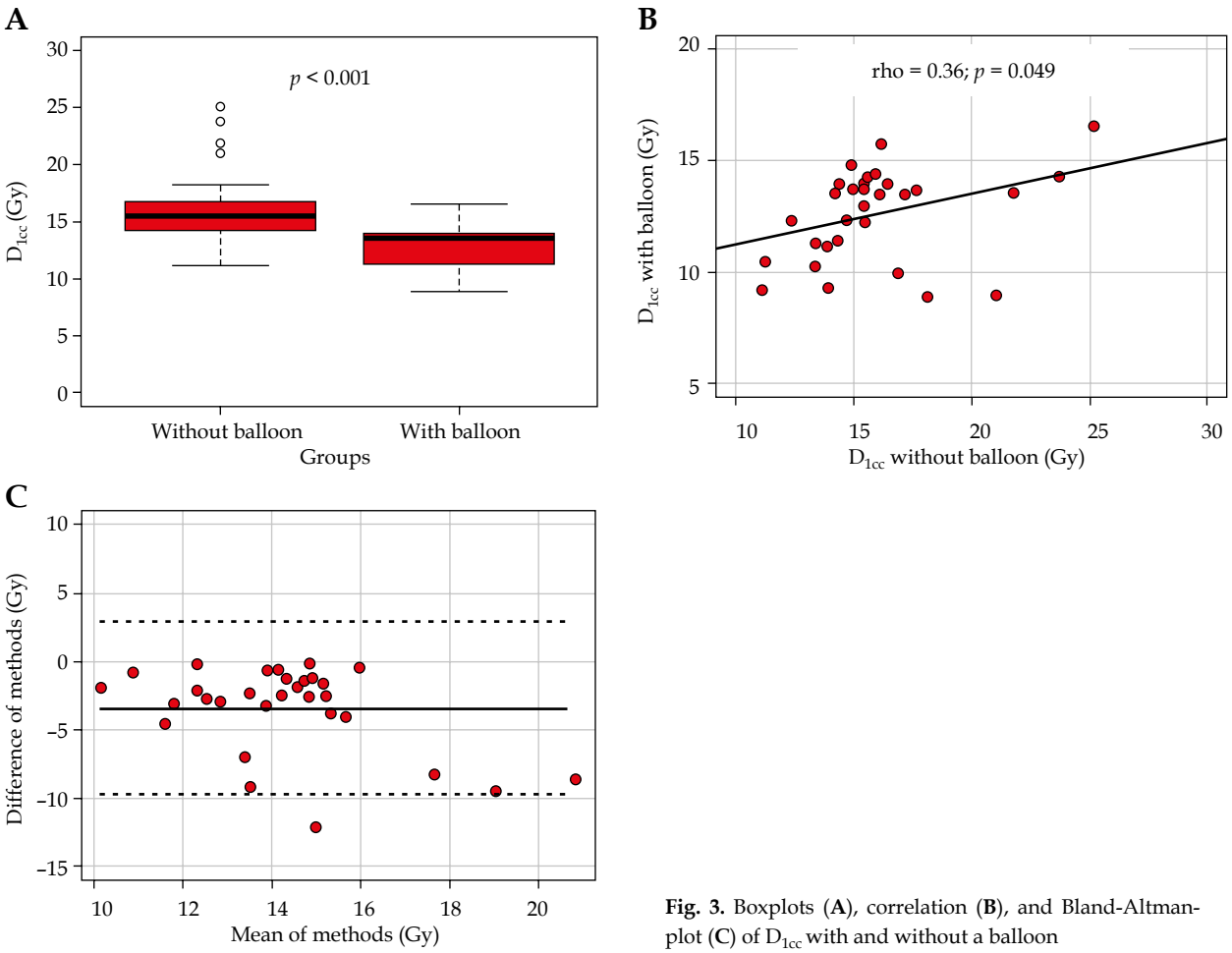


Fig. 3. Boxplots (**A**), correlation (**B**), and Bland-Altman-plot (**C**) of D_{1cc} with and without a balloon

ipated OAR without a balloon (mean, 16 Gy; deviation, 11.1 to 25.1 Gy; median, 15.5 Gy; IQR, 14.3 to 16.7 Gy; Figure 3A). The corresponding median relative difference was –16.3% (IQR, –23.2 to –8.9%), ranging from –57.3% to –0.7% (Table 4). Figures 3A and 3B shows the correlation of D_{1cc} with and without a balloon, with a Spearman's correlation coefficient of 0.36 ($p = 0.049$). Comparing both methods with Bland-Altman, analysis revealed 95% limits of agreement of –9.6 Gy to 2.9 Gy, with a mean of –3.4 Gy (Figure 3C).

Acute side effects and late morbidity

The additional balloon catheter was tolerated very well by all patients. Serious acute complications (e.g., bleeding) did not occur in any case. During the further course, 4 late complications in 3 patients (1 × abscess, 2 × gastric ulcers, 1 × non-classic radiation-induced liver disease [RILD]) were observed. Complications are described in detail in Table 5.

Thus, formally the rate of significant late effects was 12.9% (> 2) and 6.45% (> 3), respectively. Of these, only

Table 4. Statistics: organ at risk (OAR) D_{1cc} with and without a balloon as well as absolute and relative differences

Parameter	OAR without balloon D_{1cc} (Gy)	OAR with balloon D_{1cc} (Gy)	Difference absolute (Gy)	Difference relative (%)
Mean	16.0	12.6	–3.4	–19.4
SD	3.2	2.0	3.1	14.5
Median	15.5	13.5	–2.5	–16.3
25th percentile	14.3	11.2	–3.9	–23.2
75th percentile	16.7	14.0	–1.4	–8.9
Minimum	11.1	8.9	–12.1	–57.3
Maximum	25.1	16.5	–0.1	–0.7

Table 5. Side effects

Acute and late side effects according to CTCAE# v. 4.03 [1-5]	Number of cases (*n*/%)	Patient study number	Treatment/outcome	Interval between iBT and side effect
Temporarily increase of bilirubin [°1]	1/3	7	No treatment/resolved	24 h
Shivering [°1]	1/3	15	No treatment/resolved	1 h
Nausea/vomiting [°2]	2/6	29	Antiemetic drugs/resolved	1 h
Abscess [°3]	1/3	20	Drainage and antibiotics/resolved	8 weeks
Non classic RILD## (previous SIRT*) [°3]	1/3	7	Ursodeoxycholic acid/resolved	12 weeks (18 weeks after radioembolization)
Ulcus ventriculi** [°4]	1/3	20	Gastrectomy/resolved	14 weeks
Ulcus ventriculi*** [°5]	1/3	11	Gastrectomy/death	15 weeks

*#common terminology criteria for adverse events, ##radiation-induced liver disease (RILD), *selective interne radiotherapy (SIRT), **patient with significantly increased cumulative exposition of gastric mucosa, ***patient with pre-existing chronic gastritis, long-term avastin-based and/or anticoagulation treatment, severe diabetes mellitus*

in one case (3.22%, patient no. 20) a severe adverse event (SAE) can be suspected due to repeated radiation exposure of the gastric mucosa. Patient no. 11 suffered from diabetes mellitus and pre-existing chronic gastritis, and received long-term treatment with Avastin® (Bevacizumab, Roche Pharma AG, Grenzach-Wyhlen, Germany) and anticoagulation, whereas patient no. 7 underwent a radio-embolization 18 weeks prior to RILD.

Discussion

The data of this study demonstrate that the interventional application of one or two balloon catheter(s) into the connective tissue layer between the hepatic capsule and adjacent OAR generates a distance between subcapsular tumor lesion of the liver and OAR, resulting in a significant median reduction of dosage exposition of the adjacent OAR of about 16%. This effect enlarges the therapeutic "window" and consecutively, the CTV can be treated with a higher, thus presumably more efficient irradiation dose.

The current ESMO guideline for the treatment of metastatic colorectal cancer (CRC) [8] indicates the growing acceptance of minimally invasive methods for the treatment of oligo-metastases. The so-called "toolbox of minimally invasive methods" is particularly important because a significant proportion of patients with oligo-metastases are not resectable for various reasons [22]. However, in addition to the indisputable role of systemic treatment [23], local control is the key to potentially sustained improvement in the overall prognosis.

Modern irradiation techniques (e.g., stereotactic body radiotherapy [SBRT], iBT) enable precise application of very high single doses. In this regard, in addition to the tumor cell destruction mechanisms based on DNA damage, further effective radiobiological effects can be initiated [24,25]. Though, even the most accurate dose application can be limited by the proximity of sensitive OAR. Chang *et al*. [26] reported a rate of ≥ 3 toxicity of 10% (mainly gastrointestinal [GI] ulceration) after 25 Gy single fraction SBRT for unresectable pancreatic adenocarcinoma, within adjacent stomach and further GI structures.

The concept of simultaneously integrated protection (SIP) could be a conceivable strategy to avoid high doses to an OAR [27]. Whether this is associated with an increased rate of local recurrences is yet to be seen. This question is currently being examined by a prospective clinical study. Therefore, the possibility of increasing distance of the CTV to surrounding OAR appears promising.

In recent years, various groups [28,29,30] have tested feasibility, safety, and application effect of absorbable polyethylene glycol (PEG) to increase the distance between the prostate and the rectal wall. In fact, by applying PEG, a dosimetrically effective distancing can be achieved.

Thus, higher irradiation doses in patients with prostate cancer can be accomplished without an increased risk of chronic side effects onto the rectal wall. Considering this successful principle of distancing, the analysis presented here verified the feasibility, tolerability, safety, and efficacy of a balloon catheter-based approach.

As a limitation, direct comparison of both approaches, with regard to acute side effects and late toxicities is difficult, since the affected OAR within the pelvis region on one hand and the abdominal cavity on the other have different tolerance doses and, moreover, the total and single doses of the irradiation concepts are not comparable.

In addition, in recent years, numerous studies have been published regarding interstitial brachytherapy of the liver [12,13,30,31,32,33,34,35,36]. The rate of side effects ≥ 3 listed in these studies was approximately 5%.

In contrast, the rate of late toxicities ≥ 3 (12.9%) in this study appears to be higher in comparison to the cited studies. Can one or two additionally applied balloon catheter(s) cause this difference? This is rather unlikely because in the affected patients, the pre-treatment modes

(selective internal radiotherapy, surgical procedures, chemotherapy, repeated irradiation) as well as severe co-morbidities (insulin-dependent diabetes mellitus, chronic gastritis etc.) must be taken into consideration. Moreover, the intraoperative situs of the second (gastrectomized) patient (no. 11) also showed a recurrent liver metastasis, which had infiltrated and damaged a large area of the wall of the reconstructed upper GI tract.

Thus, the iBT (plus balloon)-related complication rate summarizing all side effects ≥ 3 (according to CTCAE v. 4.0) would be formally 3% (patient no. 20 with ulcer 4).

A further limitation of the study is the moderate number of cases and the retrospective and monocentric character of the analysis. In addition, the balloon catheters used are not optimal because they cannot distance the adjacent OARs in large space, only in very circumscribed areas. However, as far as known, there is currently no report on increasing the distance between tumor lesion and adjacent OAR by balloon catheter(s).

For optimization, reusable balloon catheters should be designed to be inflated and deflated when in position. In order to avoid selection bias, the results of this analysis should be examined in a prospective, possibly multicenter study.

Conclusions

Insertion of balloon catheters to increase the distance between subcapsular liver malignomas and adjacent OAR is feasible, low-risk (i.e., safe), and minimally invasive to significantly reduce the radiation dose exposure of the affected OAR due to iBT. This distancing of the adjacent OAR allows a higher D_{100} value of the CTV, therefore allowing for more efficient local control. Consequently, efficacy and sustainability of radio-ablative procedures can be increased.

During a short-term single-fraction iBT, an additional balloon catheter is well tolerated. Whether the insertion of such a catheter would also be possible for a longer period of several days within a fractional SBRT (several days) is currently still not investigated by a systematic study approach.

Thus, the insertion of a balloon catheter in cases with close-fitting OAR, which also overcomes the limitations of percutaneous, non-interventional SBRT, should be further discussed and more extensively proven as an additional option.

Addendum

This work has been conducted without research support.

Results of an interim analysis of this study with 20 patients were presented at the DEGRO-Congress (Hamburg) in 2015, final results at the ESTRO-Congress in Barcelona 2018.

Disclosure

Authors report no conflict of interest.

Dr. Hass reports personal fees from Merck Serono and BMS outside the submitted work.

Dr. Seidensticker reports personal fees from Bayer, grants and personal fees from SIRTEX Medical, personal fees from Cook Medical, personal fees from BTG, outside the submitted work.

References

1. Hellmann S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995; 13: 8-10.
2. Hughes KS, Rosenstein RB, Songhorabodi S et al. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of long-term survivors. *Dis Colon Rectum* 1988; 31: 1-4.
3. Pawlik TM, Scoggins CR, Zorzi D et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005; 241: 715-722.
4. House MG, Ito H, Gönen M et al. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. *J Am Coll Surg* 2010; 210: 744-752.
5. Weichselbaum RR, Hellmann S. Oligometastases revisited. *Nat Rev Clin Oncol* 2011; 190: 378-382.
6. Simmonds PC, Primrose JN, Colquitt JL et al. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer* 2006; 10: 982-999.
7. Hass P, Mohnike K. Extending the frontiers beyond thermal ablation by Radiofrequency Ablation: SBRT, Brachytherapy, SIRT. *Visc Med* 2014; 30: 245-252.
8. Van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; 27: 1386-1422.
9. Dawson LA. Overview: Where does radiation therapy fit in the spectrum of liver cancer local-regional therapies? *Semin Radiat Oncol* 2011; 21: 241-246.
10. Schefter TE, Kavanagh BD. Radiation therapy for liver metastases. *Semin Radiat Oncol* 2011; 21: 264-270.
11. Rusthoven KE, Kavanagh BD, Gardenes H et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* 2009; 27: 1572-1578.
12. Ricke J, Wust P, Stohlmann et al. CT-guided interstitial brachytherapy of liver malignancies alone or in combination with thermal ablation: Phase I-II results of a novel technique. *Int J Radiat Oncol Biol Phys* 2004; 58: 1496-1505.
13. Ricke J, Mohnike K, Pech M et al. Local response and impact on survival after local ablation of liver metastases from colorectal carcinoma by computed tomography-guided high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2010; 78: 479-485.
14. Bretschneider T, Ricke J, Gebauer B et al. Image-guided high-dose-rate brachytherapy of malignancies in various inner organs – technique, indications, and perspectives. *J Contemp Brachytherapy* 2016; 8: 251-261.
15. Streitparth F, Pech M, Bohmig M et al. In vivo assessment of the gastric mucosal tolerance dose after single fraction, small volume irradiation of liver malignancies by computed tomography-guided, high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2006; 65: 1478-1486.
16. Wieners G, Mohnike K, Peters N et al. Treatment of hepatic metastases of breast cancer with CT-guided interstitial brachytherapy – a phase II-study. *Radiother Oncol* 2011; 100: 314-319.
17. Timmermann RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. *Semin Radiat Oncol* 2008; 18: 215-222.
18. Herfarth KK, Debus J, Lohr F et al. Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. *J Clin Oncol* 2001; 19: 164-170.

19. Sterzing F, Brunner TB, Ernst I et al. Stereotactic body radiotherapy for liver tumors. *Strahlenther Onkol* 2014; 190: 872-881.
20. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; 143: 29-36.
21. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307-310.
22. Misiakos EP, Karidis NP, Kouraklis G. Current treatment for colorectal liver metastases. *World J Gastroenterol* 2011; 17: 4067-4075.
23. Stein A, Schmoll HJ. Systemic treatment of liver metastases from colorectal cancer. *Ther Adv Med Oncol*. 2013; 5: 193-203.
24. Brown JM, Koong AC. High-dose single-fraction radiotherapy: exploiting a new biology? *Int J Radiat Oncol Biol Phys* 2008; 71: 324-325.
25. Murray D, McBride WH, Schwartz JL. Radiation biology in the context of changing patterns of radiotherapy. *Radiat Res* 2014; 182: 259-272.
26. Chang DT, Schellenberg D, Shen J et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer* 2009; 115: 665-672.
27. Brunner TB, Nestle U, Adebahr S et al. Simultaneous integrated protection: A new concept for high-precision radiation therapy. *Strahlenther Onkol* 2016; 192: 886-894.
28. Song DY, Herfarth KK, Uhl M et al. A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during IMRT for prostate cancer: Analysis of dosimetric outcomes. *Int J Radiat Oncol Biol Phys* 2013; 87: 81-87.
29. Uhl M, van Triest B, Eble MJ et al. Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: Results of a multi-institutional phase II trial. *Radiother Oncol* 2013; 106: 215-219.
30. Pinkawa M, Berneking V, König L et al. Hydrogel injection reduces rectal toxicity after radiotherapy for localized prostate cancer. *Strahlenther Onkol* 2017; 193: 22-28.
31. Mohnike K, Wolf S, Damm R et al. Radioablation of liver malignancies with interstitial high-dose-rate brachytherapy: Complications and risk factors. *Strahlenther Onkol* 2016; 192: 288-296.
32. Tselis N, Chatzikonstantinou G, Kolotas C et al. Computed-tomography-guided interstitial high dose rate brachytherapy for centrally located liver tumour: a single institution study. *Eur Radiol* 2013; 23: 2264-2270.
33. Mohnike K, Wieners G, Schwartz F et al. Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: Safety, efficacy and effect on survival. *Int J Radiat Oncol Biol Phys* 2010; 78: 172-179.
34. Bretschneider T, Mohnike K, Hass P et al. Efficacy and safety of image-guided interstitial single fraction high-dose-rate brachytherapy in the management of metastatic malignant melanoma. *J Contemp Brachytherapy* 2015; 2: 154-160.
35. Sharma DN, Thulkar S, Sharma S et al. High-dose-rate interstitial brachytherapy for liver metastases: first study from India. *J Contemp Brachytherapy* 2013; 5: 70-75.
36. Sharma DN, Thulkar S, Kumar R et al. Interstitial brachytherapy for liver metastases and assessment of response by positron emission tomography: a case report. *J Contemp Brachytherapy* 2010; 2: 114-116.

Veröffentlichung 20

Prospective evaluation of CT-guided HDR brachytherapy as a local-ablative treatment for renal masses: a single-arm pilot trial.

Damm R, Streitparth T, Hass P, Seidensticker M, Heinze C, Powerski M, Wendler JJ, Liehr UB, Mohnike K, Pech M, Ricke J

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ORIGINAL ARTICLE

Prospective evaluation of CT-guided HDR brachytherapy as a local ablative treatment for renal masses: a single-arm pilot trial

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Abstract

Purpose In this pilot trial, we investigate the safety of CT-guided high-dose-rate brachytherapy (HDR-BT) as a local ablative treatment for renal masses not eligible for resection or nephrectomy.

Methods We investigated renal function after irradiation by HDR-BT in 16 patients (11 male, 5 female, mean age 76 years) with 20 renal lesions (renal cell carcinoma $n = 18$; renal metastases $n = 2$). Two patients had previous contralateral nephrectomy and two had ipsilateral partial nephrectomy. Six lesions had a hilar localization with proximity to the renal pelvis and would have not been favorable for thermal ablation. Renal function loss was determined within 1 year after HDR-BT by renal scintigraphy and laboratory parameters. Further investigations included CT and MRI every 3 months to observe procedural safety and local tumor control. Renal function tests were analyzed by Wilcoxon's signed rank test with Bonferroni–Holm correction of *p*-values. Survival and local tumor control underwent a Kaplan–Meier estimation.

Results Median follow-up was 22.5 months. One patient required permanent hemodialysis 32 months after repeated HDR-BT and contralateral radiofrequency ablation of multifocal renal cell carcinoma. No other patient developed a significant worsening in global renal function and no gastrointestinal or urogenital side effects were observed. Only one patient died of renal tumor progression. Local control rate was 95% including repeated HDR-BT of two recurrences.

Conclusion HDR-BT is a feasible and safe technique for the local ablation of renal masses. A phase II study is recruiting to evaluate the efficacy of this novel local ablative treatment in a larger study population.

Keywords Renal cell cancer · Brachytherapy · Local-ablative treatment · Renal tumors · Renal function

Prospektive Evaluation der CT-gesteuerten HDR-Brachytherapie als lokalablative Behandlung von Nierenraumforderungen: eine einarmige Pilotstudie

Zusammenfassung

Ziel In dieser Pilotstudie wurde die Sicherheit der computertomographie-(CT-)geführten „High-dose-rate"-Brachytherapie (HDR-BT) bei der lokalablativen Behandlung von nichtresektablen Nierenraumforderungen untersucht.

Availability of data and materials All relevant data regarding the study conclusion are displayed in the publication. Raw data used and/or analyzed during the study are available from the corresponding author on reasonable request.

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Methoden Es wurde die Nierenfunktion von 16 Patienten (11 männlich, 5 weiblich, mittleres Alter 76 Jahre) mit 20 Nierenläsionen (Nierenzellkarzinom $n=18$; Nierenmetastasen $n=2$) nach Bestrahlung mittels HDR-BT untersucht. Jeweils 2 Patienten hatten eine vorangegangene kontralaterale Nephrektomie bzw. ipsilaterale Teilresektion. Sechs Läsionen lagen zentral am Nierenbecken und waren technisch nicht suffizient durch eine thermische Ablation behandelbar. Die Nierenfunktion wurde innerhalb eines Jahres nach HDR-BT durch Nierensequenzszintigraphien sowie Laborwerte bestimmt. Weitere Untersuchungen beinhalteten CT und Magnetresonanztomographie (MRT) alle 3 Monate zur Beobachtung der Sicherheit und Tumorkontrolle. Die Nierenfunktionstests wurden mit dem Wilcoxon-Test mit Bonferroni-Holm-Korrektur der p-Werte analysiert. Überleben und lokale Tumorkontrolle wurden mit der Kaplan-Meier-Schätzung ausgewertet.
Ergebnisse Das mediane Follow-up betrug 22,5 Monate. Ein Patient benötigte permanente Hämodialyse 32 Monate nach wiederholter HDR-BT und kontralateraler Radiofrequenzablation bei multifokalem Nierenzellkarzinom. Keine weiteren Patienten zeigten eine signifikante Verschlechterung der globalen Nierenfunktion. Es wurden keine gastrointestinalen oder urogenitalen Nebenwirkungen beobachtet. Ein Patient verstarb durch lokale Tumorprogression. Die lokale Kontrollrate betrug – einschließlich wiederholter HDR-BT von zwei Rezidiven – 95%.
Schlussfolgerung Die HDR-BT ist eine technisch machbare und sichere Technik zur lokalen Ablation von Nierentumoren. Momentan rekrutiert eine Phase-II-Studie eine größere Patientenpopulation, um die Effektivität dieser neuen Anwendung genauer zu untersuchen.

Schlüsselwörter Nierenzellkarzinom · Brachytherapie · Lokalablative Behandlung · Nierentumore · Nierenfunktion

Introduction

Patients with locally confined renal masses will most likely undergo partial or total nephrectomy if clinically eligible [1]. However, up to 25% percent of patients might present with a contraindication to surgery [2]. In these cases, local therapies such as radiofrequency ablation (RFA), cryoablation (CA), or microwave ablation (MWA) are an alternative option with less treatment-associated morbidity [3, 4].

Computed tomography-guided interstitial high-dose-rate brachytherapy (HDR-BT) is an ablation technique utilizing single-fraction irradiation by an iridium-192 source which is inserted in the tumor via percutaneously applied catheters. In contrary to thermal ablation techniques, HDR-BT has no technical restriction in terms of tumor size or proximity to larger vessels or heat-vulnerable structures [5–7].

The most common application of CT-guided HDR-BT today is the radioablation of primary and secondary liver malignancies, especially hepatocellular carcinoma and colorectal liver metastases [8, 9]. A recent study also investigated the application of HDR-BT to adrenal gland malignancies [10].

To our knowledge, this new local ablative technique has not yet been thoroughly evaluated for the ablation of renal masses. Thus, we initiated a phase I trial to report the feasibility and safety of HDR-BT applied for renal masses in patients not eligible for surgery.

Patients and methods

Patient cohort

The institutional review board approved the study prior to recruitment and all patients gave oral and written informed consent.

Our study comprises 16 patients with 20 renal masses (11 male, 5 female, mean age 76 years) treated by HDR-BT at the Department of Radiology. Prior clinical evaluation was conducted by the Department of Urology and feasibility to undergo surgery was omitted in all patients (inadequate clinical performance status $n=6$; imminent hemodialysis after surgery $n=5$; metastatic disease $n=5$). Tumor entities include renal cell carcinoma (RCC; $n=18$) and metastases of colorectal carcinoma (CRC; $n=1$) or hepatocellular carcinoma (HCC; $n=1$). Bilateral and multifocal RCC were present in one patient. Two patients had prior contralateral nephrectomy and ipsilateral partial nephrectomy, respectively. Concomitant kidney diseases were polycystic kidney disease ($n=1$) and horseshoe kidney ($n=1$).

In summary, inclusion criteria were:

i. renal masses with indication for local treatment (renal metastases and histologically proven or suspected renal cell cancer),
ii. ineligibility to undergo surgical treatment (see above)
iii. sufficient performance status to safely undergo interventional treatment under conscious sedation,
iv. written informed consent,

Table 1 Characteristics for all 16 patients treated on 20 renal masses

	N (%)	Mean ± SD	Range
Patient data (N = 16)			
Sex			
Male	*N* = 11 (69)	–	–
Female	*N* = 5 (31)	–	–
Age (years)	–	75.7 ± 13.0	(52–92)
Prior surgery/renal diseases	*N* = 6 (37.5)	–	–
Horseshoe kidneys	*N* = 1 (6.3)	–	–
Polycystic kidney disease	*N* = 1 (6.3)	–	–
Contralateral total nephrectomy	*N* = 2 (12.6)	–	–
Ipsilateral partial nephrectomy	*N* = 2 (12.6)	–	–
Treatment data (N = 20)			
Etiology of renal masses			
Renal cell cancer	*N* = 18 (90)	–	–
Colorectal cancer	*N* = 1 (5)	–	–
Hepatocellular Carcinoma	*N* = 1 (5)	–	–
Tumor size and location			
T1a (<4 cm)	*N* = 15 (75)	–	–
T1b (>4 cm)	*N* = 5 (25)	–	–
Cortical/parenchymal localization	*N* = 14 (70)	–	–
Central/hilar localization	*N* = 6 (30)	–	–
Tumor size	–	3.5 ± 2.1 cm	(1.2–9.4 cm)
No. of irradiation catheters	–	2.2 ± 1.0	(1–5)
Clinical target volume	–	34.8 ± 40.3 cm^3	(3.5–163.3 cm^3)
D100	–	16.37 ± 2.18 Gy	(13.44–21.6 Gy)
Primary local tumor control	*N* = 17 (85)	–	–
Secondary local tumor control	*N* = 19 (95)	–	–

Exclusion criteria included:

i. life expectancy <6 months,
ii. estimated dose exposure to organs at risk (OAR) above local clinical standards (see below)
iii. insufficient laboratory parameters for interventional treatment (hemoglobin <6.0 mmol/l, thrombocyte count <50 Gpt/l, international normalized ratio >1.5, partial thromboplastin time >50 s)

The patient characteristics are displayed in Table 1.

Radioablation by HDR brachytherapy

To place brachytherapy catheters in a renal mass, the following procedure was performed under conscious sedation using midazolam and fentanyl: The tumor was punctured percutaneously by an 18 G coaxial needle under CT fluoroscopy (Aquillion, Canon Medical Systems, Neuss, Germany). Then, a 6F angiographic catheter sheath (Terumo Radifocus® Introducer II, Terumo Europe, Leuven, Belgium) was inserted through a guide wire (Amplatz SuperStiff™, Boston Scientific, Marlborough, USA). In a last step, a 6F irradiation catheter (afterloading catheter, Primed® medical GmbH, Halberstadt, Germany) was placed inside the catheter sheath. For the treatment of larger or complex-shaped lesions, multiple catheter placements were required for a sufficient geometry of the ablation zone while reducing the radiation exposure of adjacent organs. Twenty lesions were ablated in the study, requiring a total of 43 catheter placements in 16 patients and a median of 2 catheters per lesion (range 1–5). Typical time for the interventional procedure was 10 to 40 min depending on the complexity of the lesions and percutaneous access. Pretreatment medication included an antiemetic prophylaxis consisting of 8 mg dexamethasone and 8 mg odansetron administered intravenously. A routine antibiotic prophylaxis was not required.

After catheter placement, a multi-slice CT visualized the catheter position(s) in the renal mass and the imaging data (axial slices with 3 mm thickness) was transferred to the irradiation planning system (Oncentra® Brachy, Elekta Instrument AB, Stockholm, Sweden). The gross tumor volume (GTV) was delineated in a 3D treatment plan by hand and an automated algorithm generated a 5 mm safety margin to define the clinical target volume (CTV). As the brachytherapy catheters were fixed within the tumor eliminating inaccuracy of respiratory movement, the CTV was directly adopted as the planning target volume (PTV). Ra-

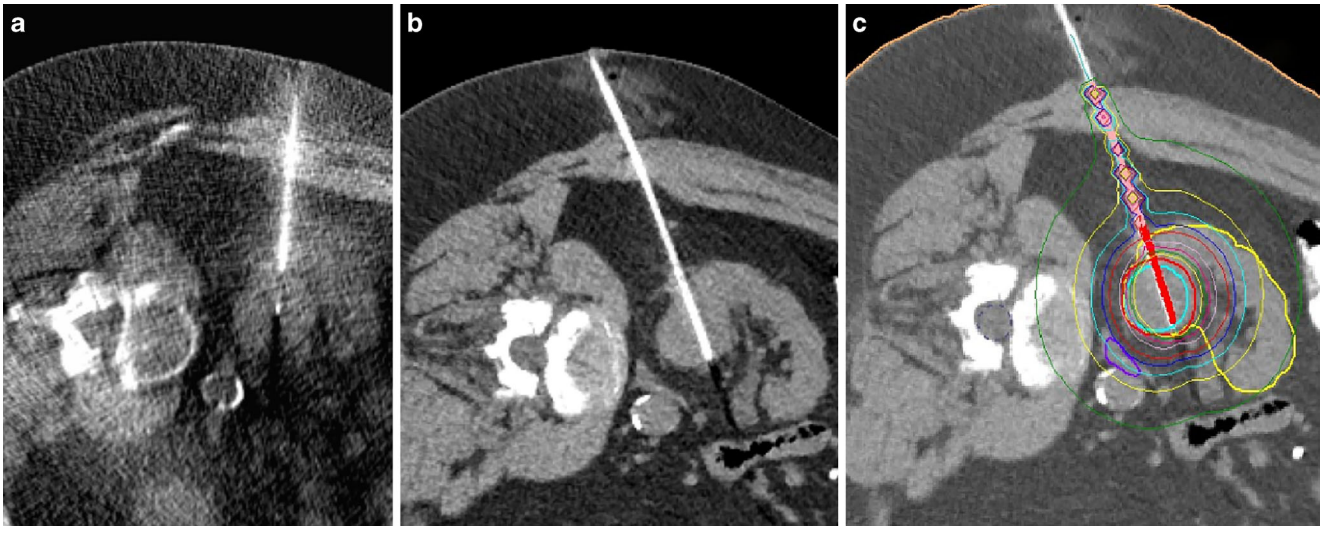

Fig. 1 Image data set of Computed tomography-guided brachytherapy for a renal cell carcinoma: **a** Computed tomography fluoroscopy, image-guided insertion of a coaxial needle for biopsy and subsequent catheter placement; **b** diagnostic computed tomography displaying the catheter sheath within the renal mass; **c** irradiation plan depicting the tip of the iridium-192 source (*red line*) and corresponding isodoses for radioablation

dioablation was then achieved by a single fraction of 15 Gy prescribed to the PTV [11]. In local recurrences of a previously irradiated lesion, a dose escalation for the PTV with 20 Gy was applied [12]. Dose constraints for organs at risk (OAR) were $D_{1CC} \leq 14$ Gy for stomach and small bowel, $D_{1CC} \leq 18$ Gy for large bowel and $V_{5Gy} \leq 66\%$ for the liver, referring to contemporary literature [13–15].

After completion of the irradiation procedure, catheters and sheaths were removed, leaving a gelatin sponge in the catheter path to prevent bleeding. Patients continued fasting and bed rest for at least 4 h. To exclude early complications, ultrasonography of the treatment area was conducted 1 to 2 h after catheter removal. Scheduled hospitalization was 2 days after treatment. Post-treatment workup included standard laboratory evaluation prior to discharge. Interventional complications were recorded and assessed by the Clavien–Dindo classification [16], radiation-induced adverse events were classified by the Common Terminology Criteria for Adverse Events (CTCAE 4.02).

A typical imaging data set for HDR brachytherapy is depicted in Fig. 1.

Imaging

Pretreatment planning was performed by magnetic resonance imaging (MRI) of the kidneys comprising high resolution T1 and T2 sequences (with and without fat saturation) as well as dynamic contrast-enhanced studies. Additional tumor sites were assessed by contrast-enhanced computed tomography (CT) of the thorax and abdomen.

During follow-up, all patients were scheduled for MRI of the kidneys every 3 months and additional CT if necessary. All imaging datasets were then reviewed for local and locoregional recurrences.

Renal function tests

Primary endpoint of the study was renal function loss within 1 year after HDR-BT.

Laboratory evaluations were conducted prior to CT-guided HDR-BT as well as 3 days, 3 months, 6 months, and 12 months after treatment, including creatinine serum levels with calculation of the estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKI-EPI) formula. Furthermore, patients underwent dynamic renal scintigraphy with technetium-99 mercaptoacetyltriglycine (Tc99m-MAG3) for determination of the tubular extraction rate (TER) at baseline and 3 months, 6 months, and 12 months after HDR-BT. The tracer extraction was quantified separately for both kidneys to assess the ipsilateral and contralateral effects of radiation exposure by HDR-BT on renal function.

Statistical analysis

Statistical analysis of all data was performed using IBM SPSS Statistics 22.0® (IBM Corp., Armonk, NY, USA). Measures for safety (e.g., acute and chronic adverse events) and efficacy (e.g., technical success) underwent descriptive statistics. Survival and local tumor control were calculated by the Kaplan–Meier estimation. All renal function tests were processed as non-parametric variables and testing was performed utilizing Wilcoxon's signed rank test with Bonferroni-Holm correction. All tests were carried out two-

sided. In data interpretation, $p \leq 0.05$ was determined as statistically significant.

Results

Treatment characteristics

Besides two renal metastases (CRC $n = 1$; HCC $n = 1$), all incidental lesions were proven histologically by prior or concomitant core needle biopsy as renal cell carcinomas (RCC $n = 18$). Local tumor stage was T1a (<4 cm) in 15 lesions and T1b and greater (>4 cm) in 5 lesions. Six lesions had a central localization in or close to the renal hilum and were not eligible for thermal ablation.

Mean tumor size was 3.5 cm (range 1.2–9.4 cm), requiring a mean number of 2 catheters for sufficient dose application (range 1–5). Including a 5 mm safety margin, a mean effective tumor-surrounding dose (CTV/D100) of 16.37 ± 2.18 Gy was achieved. Mean irradiation time was 1325 ± 858 s (22.1 ± 14.3 min).

Concomitant treatments were Y90 radioembolization for liver-dominant metastatic colorectal cancer ($n = 1$) or synchronous liver metastases of RCC ($n = 1$). One patient underwent prior HDR-BT for multifocal hepatocellular carcinoma in liver cirrhosis.

A summary of patient and treatment characteristics is given in Table 1.

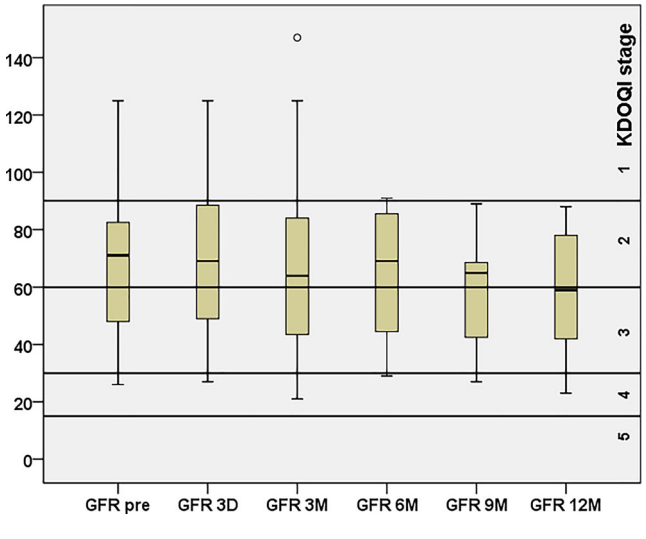

Fig. 2 Boxplots representing eGFR (ml/min) at baseline (*GFR pre*) and 3 days (*GFR 3D*), 3 months (*GFR 3M*), 6 months (*GFR 6M*), 9 months (*GFR 9M*), and 12 months (*GFR 12M*) after HDR-BT; *reference lines* depict corresponding KDOQI stages

Renal function analysis

The glomerular filtration rate was assessed by laboratory evaluation of serum creatinine (eGFR, estimated GFR according to the CKI-EPI formula) at baseline and 3 days after CT-guided brachytherapy, as well as every 3 months during follow-up. Medians of eGFR demonstrated a decrease from 71 ml/min (range 26–125 ml/min) at baseline to 58 ml/min (23–88 ml/min) after 12 months as demonstrated by the boxplot in Fig. 2. The reduction of eGFR after HDR-BT did not meet statistical significance at any time point (Wilcoxon signed rank test with Bonferroni–Holm correction). The corresponding KDOQI stages had a median of 2 from baseline to 9 months follow. At 12 months, the median KDOQI stage decreased to 3 without statistical significance ($p = 0.315$). An overview of eGFR and KDOQI stages is given in Fig. 2.

Tubular excretion rate was determined by renal scintigraphy (TER) at baseline and 3 months, 6 months, and 12 months after HDR-BT. Medians for TER decreased from 156 ml/min (range 97–340 ml/min) at baseline to a minimum of 108 ml/min (range 108–142 ml/min) at 12 months

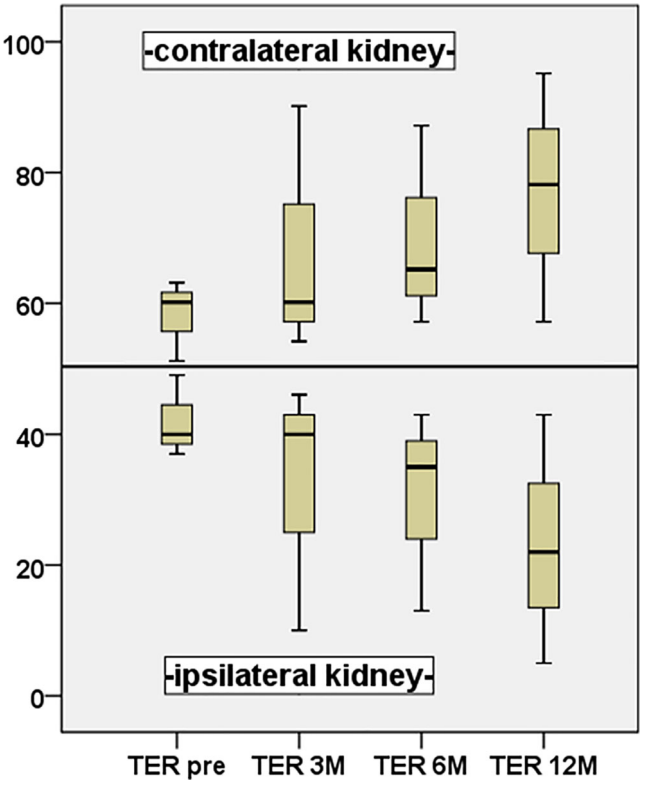

Fig. 3 Boxplots representing TER (ml/min) at baseline (*TER pre*), 3 months (*TER 3M*), 6 months (*TER 6M*), and 12 months (*GFR 12M*) after HDR-BT separated by ipsilateral (HDR-BT of renal mass) and contralateral kidney. *Reference line* represents 50 ml/min to visualize the stepwise decrease in ipsilateral kidney function after HDR-BT and compensatory increase of contralateral kidney function

follow-up. Correspondingly, median ipsilateral TER was reduced from 52 ml/min (range 37–100 ml/min) at baseline to 33 ml/min (range 5–100 ml/min) at 12 months follow-up ($p = 0.285$). The median contralateral TER demonstrated an increase from 51 ml/min (range 38–63 ml/min) to a maximum of 95 ml/min (range 57–95 ml/min) 12 months after HDR-BT ($p = 0.285$). A summary of ipsilateral and contralateral TER measurements is depicted in Fig. 3.

Clinical risk assessment

In our cohort, one puncture-related adverse event was observed in a patient suffering hematothorax from bleeding of an intercostal artery. The patient underwent subsequent ligation and was monitored for 24 h at the intensive care unit (ICU). The patient received 600 ml of packed red blood cells during surgery and antibiotic prophylaxis with ampicillin/sulbactam for 7 days. This single event was rated as grade IIIb according to the Clavien–Dindo classification and results in a patient-based risk of 6.3% and lesion-based risk of 5% for 30-day morbidity. No 30-day mortality or re-hospitalization was observed. Median duration of hospitalization was 2 days (range 2–9 days). Chronic adverse events occurred in one patient requiring permanent hemodialysis 32 months after HDR-BT with prior RFA of the contralateral kidney and a baseline eGFR of 26 ml/min. All other patients retained sufficient renal function and did not require hemodialysis during follow-up. Furthermore, no significant gastrointestinal or urogenital side effects (CTCAE grade 3/4 events) or infectious complications were observed after treatment. Overall, the patient-based risk of chronic adverse events was 6.3%.

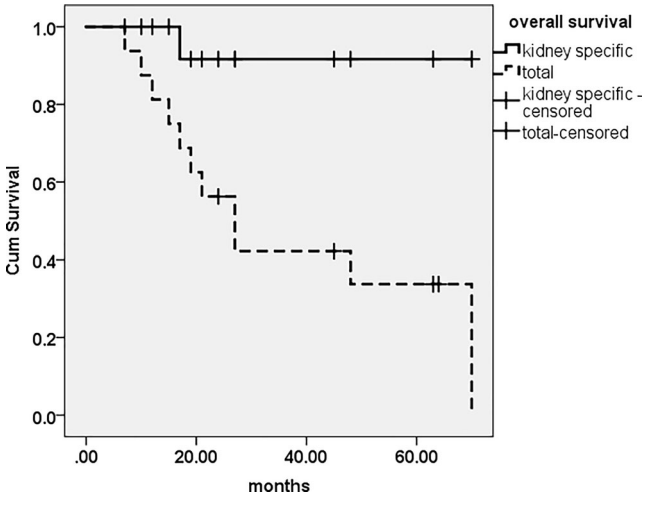

Fig. 4 Kaplan–Meier estimation for overall survival; *lines* represent any causes of death: *dotted line* including extra-renal causes, e.g., cardiovascular events, versus kidney-related causes of death (*solid line*), e.g., tumor progression of renal cell carcinoma. Median follow-up for survival was 22.5 months

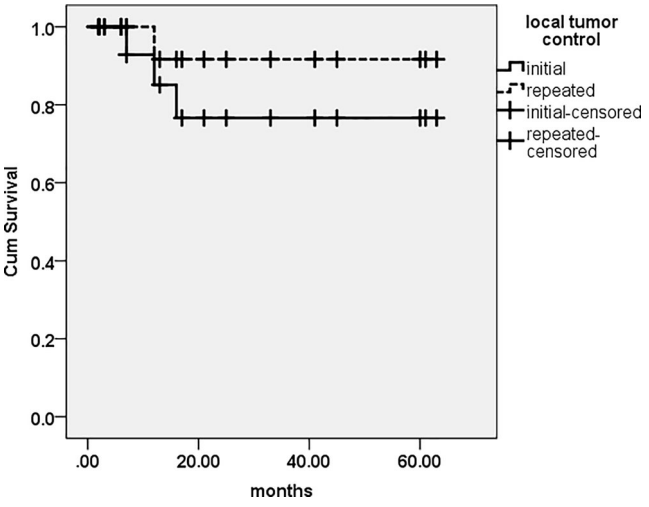

Fig. 5 Local tumor control for initial HDR-BT (85%) and additional HDR-BT in 2 cases of local recurrences (95%). Median follow-up for imaging was 14.5 months

Survival and local tumor control

Median overall survival was 27.0 months. Censoring extrarenal causes of death (malignant disease in other organs $n = 4$; aftermath of a fall in elderly patients $n = 2$; cardiopulmonary events $n = 1$; intracranial bleeding $n = 1$), the median of overall survival was not reached and mean overall survival accounted for 65.6 months. The Kaplan–Meier chart for survival is displayed in Fig. 4.

Local tumor control after CT-guided HDR-BT was reviewed throughout a median imaging follow-up of 14.5 months. Local recurrence was defined as tumor growth from baseline imaging. We observed a total of 3 local recurrences in 20 tumors, equaling a primary tumor control rate (pLTC) of 85%. Two of these recurrences were successfully treated by repeated HDR-BT, with dose escalation from 15 to 20 Gy yielding a secondary local tumor control rate of 95% (sLTC).

Figure 5 depicts the Kaplan–Meier estimation for local tumor control.

Discussion

The primary endpoint of this prospective observational trial was to assess renal function loss after CT-guided HDR-BT as a local ablative treatment for renal masses. As a secondary endpoint, we investigated procedural safety and local tumor control in HDR-BT.

Early and late adverse events

Neither acute radiation-induced effects on renal function nor any gastrointestinal side effects were observed within 30 days after HDR-BT. One heavily pretreated patient with known risk factors (treatment of bilateral tumors and severe kidney dysfunction at baseline [17]) required hemodialysis more than 2.5 years after brachytherapy. All other patients retained renal function without requiring hemodialysis during follow-up and without significant deterioration of eGFR—a benefit previously described for thermal ablation techniques [18]. In contrast, a decline in global kidney function of approximately 10% is commonly seen after partial nephrectomy and typically attributed to perioperative ischemia and nephron loss [19]. In the surgical setting, an ipsilateral decrease in renal function of up to 24.4% was reported, while contralateral compensation accounted for only 2.3% after partial nephrectomy. Correspondingly, the increase in contralateral volume was marginal [20, 21]. Our results suggest a functional hypertrophy in the contralateral kidney after CT-guided HDR-BT of ipsilateral renal masses as indicated by scintigraphic measurement of the tubular excretion rate (Fig. 3). Although these changes obviously originate from ipsilateral function loss, little is known about the specific etiology of radiation-induced nephropathy especially in single-fraction brachytherapy [22]. However, we hypothesize that the underlying mechanisms may contribute to a favorable safety profile of radioablation by HDR-BT in the kidney and our clinical follow-up implies that HDR-BT is safe in terms of global renal function.

Procedural complication rates in percutaneous radiofrequency ablation or cryoablation range from 13.0 to 23.0%, while major complications are reported in 4.3 and 4.5% of patients in larger cohorts, respectively [3, 23, 24]. Acute morbidity by CT-guided catheter placement was comparably low, including one case of puncture-associated bleeding (Clavien–Dindo grade IIIb; 6.3%).

HDR-BT compared to other ablation techniques

In our study population, one quarter of all renal masses exceeded the recommendations for thermal ablation (T1b; >4 cm) according to the recent guideline of the European Association of Urology (EAU) and nearly one third had a hilar localization that would prohibit radiofrequency ablation. Including these cases not favorable for thermal ablation techniques due to size or location, HDR-BT could demonstrate a primary local tumor control (pLTC) of 85%, and secondary tumor control (sLTC) increased to 95% after treatment of recurrences by repeated HDR-BT. In summary, local recurrence was comparable to radiofrequency ablation and cryoablation, as meta-analyses report local tumor control of 87.1 to 94.8% in small renal masses (T1a; <4 cm) and thermal ablation techniques [2, 25]. Inferior outcomes in radiofrequency ablation or cryoablation are reported for larger or central lesions [24, 26]. The LTC achieved in our study is also consistent with results of phase I/II trials investigating stereotactic body radiotherapy (SBRT) as another form of high-dose conformal irradiation in renal cell cancer (LTC ranging from 83 to 98%) [27]. Excellent results in SBRT were seen in T1a as well as T1b tumors, while toxicities were limited to grade 1 or 2 events in 18 to 78% of patients [28–30].

Advantages of SBRT include its noninvasiveness compared to the interventional approach in thermal ablation and interstitial brachytherapy, unless fiducial markers need to be placed for tumor tracking. Although procedural morbidity in interventional techniques is generally low, most reports of ablative treatments are restricted to lesions in favorable localizations, as complication rates rise with proximity to the renal pelvis [31–33]. Comparing both irradiation techniques, dose fall-off and elimination of respiratory motion by catheter fixation in single-fraction HDR-BT might reduce the impairment of healthy renal tissue while fractionating and dose distribution in SBRT might decrease radiation damage to adjacent bowel structures (comparative data only available for treatment planning in other abdominal organs) [34–36]. As HDR-BT and SBRT are not standardized in terms of dosage and fractionation, evaluation of study results is difficult.

In summery, these findings underline the potential of HDR-BT, as many technical restrictions known for thermal ablation techniques (e.g., heat-sink effect) do not apply for radioablation and no radiation-induced side effects on the renal pelvis and ureter were observed in our study. Given these technical restrictions of thermal ablation, irradiation by HDR-BT (as well as SBRT) might not only be a substitute for the ablation of small renal masses (T1a), but may present a favorable treatment for the local ablation of central or large renal tumors (T1b) compared to radiofrequency ablation or cryoablation [37, 38].

Limitations

Our study comprises only a small cohort of patients with predominantly higher age and pre-existing renal morbidity in more than one third. Furthermore, two patients underwent treatment for renal metastases as a part of systemic dissemination in advanced tumors. Hence, our study population might have been more susceptible to adverse events. Thus, safety seems to be favorable in CT-guided HDR-BT based on the presented clinical data. As tumor control might not last in all patients and statistical analysis of cofactors (e.g., tumor stage) cannot be conducted in our small cohort, upcoming investigations should focus on long-term follow-

up and a dedicated analysis of efficacy depending on tumor size (T1a vs. T1b).

Conclusion

CT-guided HDR-BT is a feasible technique for the local ablation of renal masses with encouraging results for safety and local tumor control, even in masses not eligible for thermal ablation. A phase II study is currently recruiting to evaluate the efficacy of this novel local ablative treatment in a larger study population.

Compliance with ethical guidelines

Conflict of interest R. Damm, T. Streitparth, P. Hass, M. Seidensticker, C. Heinze, M. Powerski, J.J. Wendler, U.B. Liehr, K. Mohnike, M. Pech, and J. Ricke state that there are no competing interests and that this work has not received any funding.

Ethical standards The study was conducted in accordance with the Declaration of Helsinki. All patients included were treated at a single institution, prospective data collection and analysis was approved by the local ethics committee. All patients gave written informed consent for the collection of their medical data for scientific purposes. No personal information is included in the publication, thus no dedicated approval was required.

References

1. Kim DY, Wood CG, Karam JA (2014) Treating the two extremes in renal cell carcinoma: management of small renal masses and cytoreductive nephrectomy in metastatic disease. Am Soc Clin Oncol Educ Book e214–21. https://doi.org/10.14694/EdBook_AM.2014.34.e214
2. Thompson RH, Atwell T, Schmit G, Lohse CM, Kurup AN, Weisbrod A et al (2015) Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. Eur Urol 67:252–259
3. Rivero JR, De La Cerda J 3rd, Wang H, Liss MA, Farrell AM, Rodriguez R et al (2018) Partial nephrectomy versus thermal ablation for clinical stage T1 renal masses: systematic review and meta-analysis of more than 3,900 patients. J Vasc Interv Radiol 29:18–29
4. Sung HH, Park BK, Kim CK, Choi HY, Lee HM (2012) Comparison of percutaneous radiofrequency ablation and open partial nephrectomy for the treatment of size- and location-matched renal masses. Int J Hyperthermia 28:227–234
5. Collettini F, Schnapauff D, Poellinger A, Denecke T, Schott E, Berg T et al (2012) Hepatocellular carcinoma: computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of large (5–7 cm) and very large (⟩7 cm) tumours. Eur Radiol 22:1101–1109
6. Collettini F, Singh A, Schnapauff D, Powerski MJ, Denecke T, Wust P et al (2013) Computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT) ablation of metastases adjacent to the liver hilum. Eur J Radiol 82:e509–14
7. Vollherbst D, Bertheau R, Kauczor HU, Radeleff BA, Pereira PL, Sommer CM (2017) Treatment failure after image-guided percutaneous radiofrequency ablation (RFA) of renal tumors—a systematic review with description of type, frequency, risk factors and management. Rofo 189:219–227
8. Mohnike K, Wieners G, Schwartz F, Seidensticker M, Pech M, Ruehl R et al (2010) Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: safety, efficacy, and effect on survival. Int J Radiat Oncol Biol Phys 78:172–179
9. Ricke J, Mohnike K, Pech M, Seidensticker M, Ruhl R, Wieners G et al (2010) Local response and impact on survival after local ablation of liver metastases from colorectal carcinoma by computed tomography-guided high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 78:479–485
10. Mohnike K, Neumann K, Hass P, Seidensticker M, Seidensticker R, Pech M et al (2017) Radioablation of adrenal gland malignomas with interstitial high-dose-rate brachytherapy: Efficacy and outcome. Strahlenther Onkol 193:612–619
11. Wieners G, Pech M, Rudzinska M, Lehmkuhl L, Wlodarczyk W, Miersch A et al (2006) CT-guided interstitial brachytherapy in the local treatment of extrahepatic, extrapulmonary secondary malignancies. Eur Radiol 16:2586–2593
12. Geisel D, Collettini F, Denecke T, Grieser C, Florcken A, Wust P et al (2013) Treatment for liver metastasis from renal cell carcinoma with computed-tomography-guided high-dose-rate brachytherapy (CT-HDRBT): a case series. World J Urol 31:1525–1530
13. Mohnike K, Wolf S, Damm R, Seidensticker M, Seidensticker R, Fischbach F et al (2016) Radioablation of liver malignancies with interstitial high-dose-rate brachytherapy: Complications and risk factors. Strahlenther Onkol 192:288–296
14. Streitparth F, Pech M, Bohmig M, Ruehl R, Peters N, Wieners G et al (2006) In vivo assessment of the gastric mucosal tolerance dose after single fraction, small volume irradiation of liver malignancies by computed tomography-guided, high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 65:1479–1486
15. Wieners G, Mohnike K, Peters N, Bischoff J, Kleine-Tebbe A, Seidensticker R et al (2011) Treatment of hepatic metastases of breast cancer with CT-guided interstitial brachytherapy—a phase II-study. Radiother Oncol 100:314–319
16. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213
17. Huang WC, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV et al (2006) Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. Lancet Oncol 7:735–740
18. Raman JD, Jafri SM, Qi D (2016) Kidney function outcomes following thermal ablation of small renal masses. World J Nephrol 5:283–287
19. Mir MC, Ercole C, Takagi T, Zhang Z, Velet L, Remer EM et al (2015) Decline in renal function after partial nephrectomy: etiology and prevention. J Urol 193:1889–1898
20. Choi KH, Yoon YE, Kim KH, Han WK (2015) Contralateral kidney volume change as a consequence of ipsilateral parenchymal atrophy promotes overall renal function recovery after partial nephrectomy. Int Urol Nephrol 47:25–32
21. Takagi T, Mir MC, Sharma N, Remer EM, Li J, Demirjian S et al (2014) Compensatory hypertrophy after partial and radical nephrectomy in adults. J Urol 192:1612–1618
22. Stewart FA, Te Poele JA, Van der Wal AF, Oussoren YG, Van Kleef EM, Kuin A et al (2001) Radiation nephropathy—the link between functional damage and vascular mediated inflammatory and thrombotic changes. Acta Oncol 40:952–957
23. Atwell TD, Schmit GD, Boorjian SA, Mandrekar J, Kurup AN, Weisbrod AJ et al (2013) Percutaneous ablation of renal masses measuring 3.0 cm and smaller: comparative local control and complications after radiofrequency ablation and cryoablation. Ajr Am J Roentgenol 200:461–466
24. Caputo PA, Zargar H, Ramirez D, Andrade HS, Akca O, Gao T et al (2017) Cryoablation versus partial nephrectomy for clinical

T1b renal tumors: a matched group comparative analysis. Eur Urol 71:111–117
25. Kunkle DA, Uzzo RG (2008) Cryoablation or radiofrequency ablation of the small renal mass: a meta-analysis. Cancer 113:2671–2680
26. Psutka SP, Feldman AS, McDougal WS, McGovern FJ, Mueller P, Gervais DA (2013) Long-term oncologic outcomes after radiofrequency ablation for T1 renal cell carcinoma. Eur Urol 63:486–492
27. Panje C, Andratschke N, Brunner TB, Niyazi M, Guckenberger M (2016) Stereotactic body radiotherapy for renal cell cancer and pancreatic cancer: literature review and practice recommendations of the DEGRO working group on stereotactic radiotherapy. Strahlenther Onkol 192:875–885
28. Pham D, Thompson A, Kron T, Foroudi F, Kolsky MS, Devereux T et al (2014) Stereotactic ablative body radiation therapy for primary kidney cancer: a 3-dimensional conformal technique associated with low rates of early toxicity. Int J Radiat Oncol Biol Phys 90:1061–1068
29. Siva S, Pham D, Kron T, Bressel M, Lam J, Tan TH et al (2017) Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: a prospective clinical trial. BJU Int 120:623–630
30. Staehler M, Bader M, Schlenker B, Casuscelli J, Karl A, Roosen A et al (2015) Single fraction radiosurgery for the treatment of renal tumors. J Urol 193:771–775
31. Filippiadis DK, Gkizas C, Chrysofos M, Siatelis A, Velonakis G, Alexopoulou E et al (2018) Percutaneous microwave ablation of renal cell carcinoma using a high power microwave system: focus upon safety and efficacy. Int J Hyperthermia 34:1077–1081
32. Su MZ, Memon F, Lau HM, Brooks AJ, Patel MI, Woo HH et al (2016) Safety, efficacy and predictors of local recurrence after percutaneous radiofrequency ablation of biopsy-proven renal cell carcinoma. Int Urol Nephrol 48:1609–1616
33. Dai Y, Covarrubias D, Uppot R, Arellano RS (2017) Image-guided percutaneous radiofrequency ablation of central renal cell carcinoma: assessment of clinical efficacy and safety in 31 tumors. J Vasc Interv Radiol 28:1643–1650
34. Fukuda S, Seo Y, Shiomi H, Yamada Y, Ogata T, Morimoto M et al (2014) Dosimetry analyses comparing high-dose-rate brachytherapy, administered as monotherapy for localized prostate cancer, with stereotactic body radiation therapy simulated using CyberKnife. J Radiat Res 55:1114–1121
35. Pennington JD, Park SJ, Abgaryan N, Banerjee R, Lee PP, Loh C et al (2015) Dosimetric comparison of brachyablation and stereotactic ablative body radiotherapy in the treatment of liver metastasis. Brachytherapy 14:537–542
36. Siva S, Pham D, Gill S, Bressel M, Dang K, Devereux T et al (2013) An analysis of respiratory induced kidney motion on four-dimensional computed tomography and its implications for stereotactic kidney radiotherapy. Radiat Oncol 8:248
37. Dib RE, Touma NJ, Kapoor A (2009) Review of the efficacy and safety of radiofrequency ablation for the treatment of small renal masses. Can Urol Assoc J 3:143–149
38. Kapoor A, Touma NJ, Dib RE (2013) Review of the efficacy and safety of cryoablation for the treatment of small renal masses. Can Urol Assoc J 7:E38–44