Aus der Klinik für Radiologie und Nuklearmedizin
der Medizinischen Fakultät
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Bildgeführte interstitielle Brachytherapie im Einsatz der multimodalen Therapie bei metastasierter Tumorerkrankung

Habilitationsschrift

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Inhaltsverzeichnis

Abkürzungsverzeichnis

°C	Grad Celsius
>	größer als
<	kleiner als
%	Prozent
3D	Dreidimensional
bspw.	beispielsweise
Bq	Becquerel
bzw.	beziehungsweise
CCC	cholangiozelluläres Karzinom
Ci	Curie
CLOCC	Chemotherapy + Local Ablation versus Chemotherapy
cm	Zentimeter
cm^3	Kubikzentimeter
CRC	kolorektales Karzinom
CT	Computertomografie
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
D100	Dosis, die 100 % einer bestimmten Struktur erhält
dl	Deziliter
DWI	Diffusion Weighted Imaging,

ECOG	East Coast Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
ERCP	Endoskopisch retrograde Cholangiopankreatikografie
ESAL	European Association for the Study of the Liver
ESMO	European Society of Medical Oncology
F	French
G	Gauge
G	Giga
GIST	Gastrointestinale Stromatumore
GI-Trakt	Gastrointestinaler Trakt
gtv	gross tumor volume
Gy	Gray
HCC	hepatozelluläres Karzinom
HDR	Hochdosisrate (High Dose Rate)
iBT	interstitielle Brachytherapie
mg	Milligramm
ml	Milliliter
mm	Millimeter
MRT	Magnetresonanztomografie
mTOR	mechanistic Target of Rapamycin
MWA	Mikrowellenablation

n	Anzahl
NCCN	National Comprehensive Cancer Network
nl	Nanoliter
p	Wahrscheinlichkeit
PDAC	duktales Adenokarzinom der Pankreas
PTT	partielle Thromboplastinzeit
PTV	Planning Target Volume
PTZ	Prothrombinzeit
RILD	Radiation Induced Liver Disease
RFA	Radiofrequenzablation
s	Sekunde
SBRT	stereotaktische perkutane Strahlentherapie
TACE	transarterielle Chemoembolisation
TER	tubuläre Extraktionsrate
TKI	Tyrosinkinase-Inhibitoren
TNM	Stadieneinteilung von malignen Tumoren (Classification of Malignant Tumours) – Tumor, Nodal (Lymphknoten), Metastasen
VEGF	Vascular Endothelial Growth Factor
vs.	versus

Vorwort

Gemäß den Ausführungsbestimmungen zur Habilitationsordnung der Otto-von-Guericke-Universität Magdeburg in der Fassung vom 26.04.2016 für eine kumulative Habilitationsschrift befasst sich die vorliegende Habilitationsschrift im Wesentlichen mit dem Inhalt der nachfolgend aufgelisteten Publikationen (Publikationen 1–12).

Publikation 1

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.

Publikation 2

Efficacy and safety of CT-guided high-dose-rate interstitial brachytherapy in primary and secondary malignancies of the pancreas.

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

Eur J Radiol. 2019 Mar;112:22-27. doi: 10.1016/j.ejrad.2018.12.020.

Publikation 3

Treatment of metastatic, imatinib refractory, gastrointestinal stroma tumor with image-guided high-dose-rate interstitial brachytherapy.

Omari J, Drewes R, Matthias M, Mohnike K, Seidensticker M, Seidensticker R, Streitparth T, Ricke J, Powerski M, Pech M.

Brachytherapy. 2019 Jan - Feb;18(1):63-70. doi: 10.1016/j.brachy.2018.09.006.

Publikation 4

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.

Publikation 5

Treatment of metastatic gastric adenocarcinoma with image-guided high-dose rate, interstitial brachytherapy as second-line or salvage therapy

Omari J, Drewes, R. Othmer M, Hass P, Ricke J, Pech M, Powerski M.

Diagn Interv Radiol. 2019 Sep;25(5):360-367. doi: 10.5152/dir.2019.18390.

Publikation 6

Interventionelle Verfahren bei metastasiertem kolorektalem Karzinom

Omari J, Seidensticker M, Ricke J

Gastroenterologie up2date 2016; 12(03): 249-261 doi: 10.1055/s-0042-114591.

Publikation 7

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.

Publikation 8

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. 2019 Jan;191(1):48-53. doi: 10.1055/a-0636-4055.

Publikation 9

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 Dec;10(6):516-521. doi: 10.5114/jcb.2018.80626.

Publikation 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.

Publikation 11

Treatment of hepatic pancreatic ductal adenocarcinoma metastases with high-dose-rate, image-guided interstitial brachytherapy: a single center experience.

Drewes R, **Omari J**, Manig M, Seidensticker M, Hass P, Ricke J, Powerski M, Pech M.

J Contemp Brachytherapy. 2019 Aug;11(4):329-336. doi: 10.5114/jcb.2019.87269. E-pub 2019 Aug 29.

Publikation 12

Efficacy and safety of percutaneous CT-guided high-dose-rate interstitial brachytherapy in the treatment of oligometastatic lymph node metastases of the retroperitoneal space.

Heinze C, **Omari J**, Manig M, Hass P, Venerito M, Damm R, Jargiello T, Ricke J, Powerski MJ, Pech M.

J Contemp Brachytherapy (noch nicht in Pubmed veröffentlicht)

1 Einleitung

1.1 Sekundäre Lebertumore

Als dem am häufigsten von Metastasen befallenen Organ im Körper wird der Leber bei der Behandlung von metastasierenden Tumorerkrankungen eine prognostisch entscheidende Rolle zugeschrieben. Ein lokaler Tumorprogress der Leber führt letztlich zum Leberversagen und hat einen negativen Effekt auf das Gesamtüberleben vom Patienten (1).

Der am häufigsten in die Leber metastasierte Tumor ist das kolorektale Karzinom. Etwa die Hälfte aller Patienten mit einem kolorektalen Karzinom hat bereits bei Diagnosestellung oder entwickelt im weiteren Verlauf der Erkrankung Lebermetastasen (2). Aber auch seltenere Entitäten wie das Magenkarzinom, Ösophaguskarzinom, Analkarzinom oder das Pankreaskarzinom metastasieren in die Leber. Insgesamt stellt die Lebermetastase noch vor den primären Lebertumoren (hepatozelluläres Karzinom [HCC] und cholangiozelluläres Karzinom [CCC]) den häufigsten Tumor der Leber dar (3). Lange Zeit galten Lebermetastasen als nicht heilbar. Dies gilt heute nur noch für den diffusen Befall der Leber. In diesem Zusammenhang kommen die Systemtherapie und nachrangig lokoregionäre Therapien (bspw. Radioembolisation) in palliativer Intention zum Einsatz.

Bei limitierten Lebermetastasen gilt die chirurgische Resektion als Goldstandard und bietet einen potenziellen kurativen Ansatz. Trotz technischer Weiterentwicklung der Leberchirurgie bleiben der operativen Vorgehensweise Limitationen gesetzt. Komorbiditäten, Anzahl, Lokalisation und Ausdehnung der Metastasen sowie nicht ausreichend vorhandenes Leberrestvolumen beschränken die Anwendung operativer Verfahren auf etwa 20–30 % der Patienten (4). Für die resezierten Patienten mit hepatischen Metastasen eines kolorektalen Karzinoms zeigte eine Analyse von Scheele et al., dass auch nach erfolgter R0-Resektion bei etwa 37 % der Patienten hepatische Rezidive im Verlauf auftreten (5). Zudem konnte in einer prospektiven Studie von Welsh et al. gezeigt werden, dass in 8,8 % (von 1005 Resektionen) eine angestrebte R0-Resektion nicht erreicht werden konnte (6). Signifikant erhöht war der R1-Resektionsstatus (35 %) nach innovativen Resektionsverfahren mit nicht anatomischer Resektion (6). Entsprechend diesen technischen und onkologischen Restriktionen rücken minimalinvasive, parenchymschonende Ablationsverfahren in den Vordergrund bei der Behandlung von Lebermetastasen.

1.2 Primäre und sekundäre Pankreastumore

Das duktale Adenokarzinom des Pankreas (PDAC) ist der häufigste maligne Pankreastumor. Die 5-Jahres-Überlebensrate liegt bei 0,5–9 % (7). Der einzige potenziell kurative Heilungsansatz ist die komplette chirurgische Resektion im Gesunden. Jedoch gibt es keine einheitliche Empfehlung dahingehend, wie weit im Gesunden reseziert werden soll.

Bei über 80 % der Patienten findet sich bereits bei Diagnosestellung ein lokal fortgeschrittenes oder metastasiertes PDAC vor, das für eine Resektion nicht geeignet ist (8). Patienten, die in kurativer Intention einer Resektion unterzogen werden, entwickeln in über 60 % innerhalb von zwei Jahren ein Rezidiv (9). Isolierte Lokalrezidive entwickeln sich in 30 % nach Pankreatikoduodenektomie (10).

Anders als Lebermetastasen sind Pankreasmetastasen ein seltenes Phänomen. Nierenzellkarzinome, Lungenkarzinome und das kolorektale Karzinom stellen am häufigsten den Primarius. Insgesamt machen Metastasen lediglich 2–5 % der Pankreastumore aus (11,12). Daraus resultieren nur begrenzte klinische Erfahrungen. Hinsichtlich der Metastasenresektion am Pankreas fehlen bis zum jetzigen Zeitpunkt verlässliche klinische Daten, die einen Vorteil im Langzeitüberleben aufzeigen.

Jedenfalls weist die Resektion von Pankreastumoren trotz der Innovationen in den Operationstechniken sowie der Fortschritte im postoperativen Management immer noch eine erhebliche postoperative Morbidität von 30–60 % auf (13). Die Krankenhaus-Mortalitätsrate wird in der Literatur mit unter 5 % beschrieben (13).

Damit stellen insbesondere bei lokal fortgeschrittenen/inoperablen Tumoren, Rezidivtumoren oder Pankreasmetastasen minimalinvasive Verfahren, wie die lokale Tumorablation, eine innovative Behandlungsoption zur lokalen Kontrolle dar.

1.3 Onkologische Motivation lokaler Therapien

Motiviert durch die Behandlungserfolge beim hepatisch metastasierten kolorektalen Karzinom steigt auch der Anreiz der lokalen Metastasentherapie bei anderen Tumorentitäten. Auch die Resektionen pulmonaler Metastasen beim Sarkom sowie die Resektionen von Hirnmetastasen beim nicht kleinzelligen Bronchialkarzinom haben bereits Einzug in die jeweiligen Leitlinien gefunden. Der Goldstandard der lokalen Metastasentherapie bleibt bis auf wenige Ausnahmen die chirurgische Resektion. Jedoch

haben bildgeführte, interventionelle radiologische Verfahren in den letzten Jahren, insbesondere in der oligometastasierten Situation, intensiv an Bedeutung gewonnen. Bildgeführte interventionelle Verfahren werden von der Europäischen Gesellschaft für medizinische Onkologie (ESMO, European Society of Medical Oncology) als etablierte lokale Therapieverfahren anerkannt. Dies gilt in besonderem Maße für die Behandlung kolorektaler Metastasen, da hierfür eine große Anzahl vorwiegend retrospektiver, aber auch prospektiver Phase-II-Kohorten-Studien vorliegt (14). Jenseits des metastasierten kolorektalen Karzinoms sowie des hepatozellulären Karzinoms wird der bildgeführten lokalen Ablation in der Metastasentherapie eher eine geringe Akzeptanz entgegengebracht. Grund hierfür ist unter anderem die nicht ausreichend belastbare Studienlage (prospektive Studien) zum Effektivitätsnachweis. Die vorliegende Arbeit umfasst unter anderem verschiedene Sicherheits- und Effektivitätsanalysen der lokalen Ablation mittels bildgeführter interstitieller Brachytherapie jenseits kolorektaler Metastasen und des hepatozellulären Karzinoms.

1.3.1 Oligometastasierung

Die onkologische Motivation der lokalen Ablation liegt neben wenigen Ausnahmen hauptsächlich darin, Fernmetastasen im Rahmen eines multimodalen Therapiekonzepts zu behandeln. Die Behandlung von Fernmetastasen stellt eine große Herausforderung für die Onkologie dar. Laut aktuellen Studienergebnissen scheint es eine Gruppe von Patienten mit günstiger Tumorbiologie zu geben, die durch eine lokale Metastasentherapie ein verlängertes progressionsfreies Überleben und Gesamtüberleben erreichen. So zeigte eine Studie von Gomez et al. beim nicht kleinzelligen Bronchialkarzinom mit maximal drei Metastasen ein signifikant verlängertes progressionsfreies Überleben für Patienten mit Erstlinien-Chemotherapie und konsolidierender lokaler Bestrahlung gegenüber Patienten mit alleiniger Erstlinien-Chemotherapie (11,9 vs. 3,9 Monate) (15). Für solches Patientenkollektiv wurde der Begriff der „Oligometastasierung“ eingeführt, eine Art intermediäres Stadium zwischen lokalisierter und systemischer Erkrankung. Das Konzept der Oligometastasierung nimmt eine kaskadenartige Hierarchie der Metastasierung an (lokales Stadium → Oligometastasierung → diffuse Metastasierung → terminale Erkrankung) (16). Dies führte zu einem radikalen Umdenken in der Welt der Onkologie. Der Duktus, demzufolge jeder metastasierte Tumor nur noch rein palliativ zu behandeln sei, wurde aufgehoben. Vielmehr haben Tumore, bei denen es lediglich zur Absiedelung einzelner Metastasen gekommen ist,

durch die vollständige Eliminierung aller Metastasen eine Heilungschance. Die Oligometastasierung ist nicht endgültig definiert. Die wohl am weitesten ausgelegte Definition findet sich in den Leitlinien der ESMO. Demnach wird der Einsatz lokaler Therapien bei „bis zu 2 oder gelegentlich 3 befallenen Organsystemen“ und „bis zu 5 oder manchmal mehr Läsionen“ zugelassen, wenn mittels lokaler Therapien eine Tumorfreiheit des Patienten erreicht werden kann (17). Die Problematik dieser unscharf parametrierten Definition ist die fehlende Berücksichtigung von Vorhersagemodellen über den weiteren Verlauf einer Tumorerkrankung. Um dieser Problematik gerecht zu werden, ist das zukünftige Ziel, mittels molekularer Subtypisierungs-Analysen den Tumorverlauf (diffus oder oligometastatisch) vorhersagen zu können. Weichselbaum und Hellman suggerieren, dass es sich beim oligometastatischen Tumor sogar um eine eigene Tumorentität handeln würde (16), für die ein eigenes Therapiekonzept, einschließlich lokaler Therapien zu erstellen sei.

1.3.2 Deepness of Response

Eine weitere onkologische Rationale der lokalen Therapie basiert auf dem Konzept der „Tiefe des Ansprechens“ (Deepness of Response). Die Deepness of Response ist definiert als die niedrigste nach einer Therapie erreichte Tumorlast beim Patienten und zeichnet sich als ein lebensverlängernder Parameter ab (18). Das Konzept basiert auf der Annahme, dass eine für den Tod verantwortliche Tumorlast (letale Tumorlast) durch zytoreduktive Maßnahmen erst zu einem späteren Zeitpunkt erreicht wird. Dieses theoretische Modell wurde zwar initial für das Ansprechen nach einer Systemtherapie bei Patienten mit metastasiertem kolorektalen Karzinom (CRYSTAL-Studie; OPUS-Studie) aufgestellt (18), dürfte aber auch auf andere zytoreduktive Therapien, wie lokalen Ablationsverfahren, zutreffen. Vielmehr noch unterstützt diese Hypothese den erweiterten Einsatz lokal ablativer Verfahren, zumal damit deutlich höhere Ansprechraten erreicht werden können als die in der Studie von Mansmann et al. beschriebenen 50 % nach Systemtherapie (18). So könnte die bei hohem Remissionsdruck zum Einsatz kommende Mehrfachkombinations-Systemtherapie, verbunden mit ihrem hohen Nebenwirkungsprofil (bspw. zum Erreichen einer sekundären kurativen Resektion), durch eine Kombinationstherapie aus lokaler Ablation und Systemtherapie ersetzt werden.

1.3.3 Multimodale Therapieansätze

Spätestens seit den Ergebnissen der CLOCC-Studie wird der Einsatz kombinierter Behandlungsansätze auch im metastasierten Tumorstadium vorangetrieben. So konnte ein Überlebensvorteil für Patienten mit metastasiertem kolorektalen Karzinom verdeutlicht werden, die zusätzlich zur Systemtherapie eine lokale Metastasentherapie (Resektion oder Radiofrequenzablation) erhalten haben (19). Ein Überlebensvorteil durch eine multimodale Therapie konnte auch in der AIO-FLOT3-Studie von Al-Batran et al., wenngleich nicht randomisiert, für Patienten mit metastasiertem Magenkarzinom erreicht werden (20). Grund hierfür könnte unter anderem das häufig zu beobachtende „gemischte Ansprechen“ (Mixed Response) nach alleiniger System-/Chemotherapie sein. Darunter versteht man ein divergiertes Ansprechen von Metastasen: Während die einen Metastasen infolge der Systemtherapie schrumpfen, weisen andere Metastasen einen Progress auf. Die Ursache hierfür liegt in der Heterogenität und Multiklonalität der Metastasen. Im Zeitalter der personalisierten Medizin mit zielgerichteter Systemtherapie stellt das Auftreten eines Mixed Responses eine immer größere Herausforderung dar. Die zielgerichtete Systemtherapie führt zur klonalen Selektion systemtherapieresistenter Tumorzellen und damit zum Progress einzelner Metastasen. Der konsolidierende Einsatz lokaler Ablationsverfahren beim Mixed Response destruiert genau diese klonalen, chemotherapieresistenten Zellen und kann damit eine Umstellung der Systemtherapie verzögern bzw. dem Patienten eine vorübergehende systemtherapiefreie Zeit gewähren.

2 Lokale Ablationsverfahren

Bei den interventionellen radiologischen Verfahren werden jene „ablativen Verfahren“ unterschieden, die mit einer vollständigen Zerstörung des Tumors das Ziel der Vollremission verfolgen, und jene „lokoregionären Verfahren“ mit dem Ziel der partiellen Remission.

Der folgende Abschnitt beschränkt sich auf die Radiofrequenzablation (RFA) sowie auf die lokalen Radiotherapien: stereotaktische perkutane Strahlentherapie (SBRT) und bildgesteuerte interstitielle Brachytherapie (iBT). Auf die lokoregionären Verfahren, zu denen die embolischen Verfahren, wie Radioembolisation und Chemoembolisation, zählen, wird in dieser Arbeit nicht weiter eingegangen.

2.1 Radiofrequenzablation

Die Radiofrequenzablation hat sich in den zurückliegenden Jahren bei Irresektabilität oder auf besonderen Patientenwunsch zur am häufigsten eingesetzten Ablationsmethode durchgesetzt. Durch einen hochfrequenten Wechselstrom wird an der zuvor bildgeführt in den Tumor positionierten Nadelelektrode ein Temperaturanstieg auf 60–100 °C erreicht. Hierdurch entsteht im Tumor sowie in der unmittelbaren Umgebung (Sicherheitssaum vom 5 mm) eine kontrollierte Koagulationsnekrose (21). Einen Paradigmenwechsel erreichte die Radiofrequenzablation in der Therapie des hepatozellulären Karzinoms. Die Metaanalyse von Majumdar et al. zeigte bei HCCs < 3 cm, dass die Radiofrequenzablation und die Resektion im Langzeitüberleben absolut ebenbürtig sind (22). Cucchetti et al. zeigten zusätzlich die Kosteneffektivität zugunsten der RFA (23). Diese Erkenntnisse wurden in der weltweit populärsten Therapieempfehlung für das HCC, den EASL Clinical Practice Guidelines, berücksichtigt und dementsprechend die RFA als First-Line-Therapie beim „very early stage HCC“ als gleichwertig zur Resektion verankert (24).

Einen weiteren Meilenstein in der lokalen Ablation von Lebermetastasen des kolorektalen Karzinoms setzen die Ergebnisse der CLOCC-Studie. Diese EORTC-Studie mit 119 Patienten belegt in ihren Langzeitergebnissen aus dem Jahr 2017 nach einem medianen Beobachtungszeitraum von 9,7 Jahren, dass das mediane Gesamtüberleben (45,6 vs. 40,5 Monate) und die 3-, 5- und 8-Jahres-Überlebensraten (56,9 %, 43,1 %, 35,9 % vs. 55,2 %, 30,3 %, 8,9 %) jeweils nach Kombinationstherapie (Che-

motherapie + lokale Therapie) signifikant besser waren als nach alleiniger systemischer Therapie (19). Eingeschlossen wurden in diese Studie nur Patienten mit nicht resektablen Lebermetastasen des kolorektalen Karzinoms.

In Tumorkonferenzen wird üblicherweise im kurativen Setting grundsätzlich die Metastasenresektion der lokalen Ablation bevorzugt, wenn auch die Resektion vergleichbare negative prognostische Faktoren aufweist: Anzahl der Metastasen, Tumorgröße und initialer Resektionsstatus haben einen negativen Einfluss auf das Überleben (25). Insbesondere bei ungünstigen Lokalisationen sowie nicht anatomischen Resektionen steigen die R1-Raten nach Resektion bis auf 35 % (6).

Einen Vergleich der lokalen Kontrollraten nach Radiofrequenzablation und chirurgischer Resektion bietet die Studie von Tanis et al. aus dem Jahr 2013. In dieser Studie wurden Patienten aus der EPOC-Studie mit hepatischer Resektion mit Patienten aus der CLOCC-Studie mit Radiofrequenzablation und gleicher systemischer Chemotherapie verglichen. Es wurden lediglich Läsionen bis 4 cm Größe herangezogen. Das Ergebnis zeigte eine nahezu übereinstimmende Rezidivrate nach Resektion und Radiofrequenzablation (6,0 % nach RFA vs. 5,5 % nach Resektion) (26). Wie aus vorherigen Studien bekannt wurde zudem gezeigt, dass die Rate an Lokalrezidiven nach RFA ab einer Tumorgröße von 3 cm signifikant steigt: Bei Läsionen über 3 cm lag die Lokalrezidivrate bei 21,4 %, bei Läsionen unter 3 cm bei 2,9 %. Interessanterweise verhielt sich die R1-Rate nach chirurgischer Resektion dem entgegengesetzt: Bei Läsionen über 3 cm lag die R1-Resektionsrate bei 0 %, bei Tumorgrößen unter 3 cm bei 6,1 % (26). Diese Ergebnisse, insbesondere der chirurgischen Resektion, sind vermutlich darauf zurückzuführen, dass Patienten mit kleinen Läsionen häufiger eine atypische Resektion mit kleinerem Sicherheitssaum erhalten, während größere Tumore mittels ausgedehnter Leberteilresektionen behandelt werden. Diese Annahme würde mit den Ergebnissen der bereits genannten Studie von Welsh et al. insofern in Einklang stehen, als insbesondere nach atypischer Resektion die R1-Resektionsrate signifikant ansteigt. In kurativer Intention ist demnach die Chirurgie der RFA insbesondere dann zu bevorzugen, wenn anatomisch reseziert werden kann. Dennoch sieht die neue S3-Leitlinie des kolorektalen Karzinoms erstmals vor, dass auch bei primär resektablen Metastasen kleiner als 3 cm alternative Verfahren wie die lokalen Ablationsverfahren unter Berücksichtigung des Allgemeinzustands angeboten und in einem interdisziplinären Tumorboard diskutiert werden sollen (27). Läsionen größer als 3 cm sollten in der Regel nicht mittels Radiofrequenzablation behandelt werden.

Weitere Limitation der Radiofrequenzablation sind angrenzende thermosensible Risikostrukturen wie Gallengänge, die Lokalisation der Metastase (hilusnah und subkapsulär), die Geometrie der Tumorläsion und Kühlungseffekte durch benachbarte Gefäße oder erhöhte Tumorvaskularisation. Die Limitationen haben einen unmittelbaren negativen Einfluss auf die lokale Kontrolle. So erhöht sich das Risiko eines Lokalrezidivs nach einer RFA um den Faktor 1,2, wenn der Abstand zwischen gewünschter Koagulationsnekrose und einem angrenzenden großen Gefäß 4 mm unterschreitet (28). Von diesen Limitationen unbeeinträchtigt sind strahlenbasierte Ablationsverfahren, die den Schwerpunkt dieser Arbeit stellen.

2.2 Bildgeführte interstitielle Brachytherapie

2.2.1 Methode

Die bildgesteuerte interstitielle Brachytherapie ist ein interdisziplinäres Verfahren zwischen der interventionellen Radiologie und der Strahlentherapie und zählt zu den hochkonformalen, hypofraktionierten strahlentherapeutischen Therapien.

In einem ersten Schritt erfolgt die Positionierung der die Strahlenquelle aufnehmenden Katheter innerhalb des zu behandelnden Tumors. Anschließend wird die Strahlenquelle innerhalb des Tumors platziert. Eine dreidimensionale Dosisplanung ermöglicht eine exakte Bestrahlung des Tumors von innen nach außen mit exorbitant hohen Dosen (< 50 Gy) im Tumorzentrum (29). Aufgrund des raschen Abfalls der Strahlendosis mit zunehmendem Abstand zur Strahlenquelle können angrenzende strahlensensible Strukturen bestmöglich geschont werden. Anders als in den ersten Anwendungen der interstitiellen Brachytherapie, im Rahmen derer die Katheter intraoperativ palpatorisch oder sonografisch platziert wurden, bietet die perkutane bildgesteuerte Positionierung des Katheters ein deutlich weniger invasives und exakteres Verfahren. Die Zielläsion wird üblicherweise unter CT-Fluoroskopie mit einer 18G-Nadel punktiert. Anschließend wird in Seldinger-Technik eine 6-F-Angioschleuse (Radifocus, Terumo, Tokyo, Japan) über einen steifen Führungsdraht (Amplatz, Boston Scientific, Marlborough, USA) eingeführt. In einem weiteren Schritt wird der Bestrahlungskatheter über die Schleuse in den Tumor eingebracht. Die Größe sowie die Lagebeziehung des Tumors zu strahlensensiblen benachbarten Strukturen bestimmen über die Anzahl der benötigten Katheter. Die eingebrachten Katheter werden mittels Hautnähten fixiert. Um die korrekte Po-

sitionierung der Katheter zu bestätigen und die Bestrahlung zu planen, erfolgt anschließend an die Katheterpositionierung eine Computertomografie (CT) mit Kontrastmittel in Atemanhaltetechnik, in welcher der Interventionalist das Gross Tumor Volume (GTV), die Katheterspitze sowie Risikostrukturen einzeichnet. In einem automatischen Algorithmus wird um das GTV ein Sicherheitssaum von 5 mm generiert. GTV plus Sicherheitssaum ergeben das Clinical Target Volume (CTV). Aufgrund der fixierten Katheterlage im Tumor entspricht das CTV unmittelbar dem Planning Target Volume (PTV) (30). Die computergestützte 3D-Bestrahlungsplanung sowie die eigentliche Bestrahlung mit einer Iridium^{192}-Quelle mit einer Nennaktivität von 10 Ci (370 GBq) in Afterloading-Technik erfolgt dann in der Strahlentherapie (Afterloading-System: Nucletron, Elektra Ab, Stockholm, Schweden). Ein wesentlicher Vorteil dieser Methode ist die semiautomatische Modulierung der Bestrahlungsgeometrie (Isodosis-Linien) an die Tumorgeometrie über die unterschiedliche Haltedauer der Strahlungsquelle an vordefinierten Positionen. Die Bestrahlung erfolgt als monofraktionäre Therapie, bei der die Iridium-Quelle etwa 40–60 Minuten im Katheter/in den Kathetern verbleibt. Unmittelbar nach dem Eingriff werden die Katheter unter Verschluss des Punktionskanals mittels resorbierbaren thrombogenen Materials (Gelfoam, Pfizer Inc, New York, USA) gezogen. Die tumorumschließende Zieldosis liegt abhängig von der Tumorentität bei 12–25 Gy.

Für die Therapie ist keine Vollnarkose notwendig. Während der Katheteranlage erhält der Patient eine Lokalanästhesie der Punktionsstelle (Lidocain) sowie eine intravenöse Analgosedierung mit Fentanyl und Midazolam, angepasst an das individuelle Gewicht und Schmerzempfinden. Zur Beobachtung der Herz-Kreislauf-Funktion wird während der gesamten Intervention ein Monitoring der Vitalparameter durchgeführt.

Nach aktueller Studienlage konnte sich die perkutane, bildgeführte interstitielle Brachytherapie als ein effektives und sicheres Verfahren in der Behandlung kolorektaler Lebermetastasen und hepatozellulärer Karzinome etablieren und wurde von der ESMO in die jeweilige Leitlinie aufgenommen (17,31). In den von uns durchgeführten Analysen konnten Effektivität und Sicherheit des Verfahrens auch auf andere Lokalisationen und Entitäten ausgeweitet werden.

So konnte in einer Analyse bei 12 Patienten mit Magenkarzinomen und insgesamt 36 Metastasen (29 Lebermetastasen, 2 Pankreasmetastasen und 5 Lymphknotenmeta-

stasen) mit einer medianen Tumorgröße von 2 cm (Range: 1–10,2 cm) und einer medianen tumorumschließenden Dosis von 19,9 Gy (Zieldosis: 20 Gy) eine lokale Kontrolle von 89 % erreicht werden **(Publikation 5)**. Es zeigten sich vier Lokalrezidive nach im Median 7 Monaten (2 Lebermetastasen, 1 Lymphknotenmetastase und 1 Pankreasmetastase) und eine CTCAE-Grad-III-Komplikation (Common Terminology Criteria for Adverse Events). Das progressionsfreie Überleben lag bei 6,6 Monaten und das mediane Gesamtüberleben bei 11,4 Monaten.

In einer weiteren retrospektiven Studie wurde die Anwendung der bildgeführten interstitiellen Brachytherapie in der Salvage-Situation bei hepatisch metastasierten Pankreas-Adenokarzinomen untersucht **(Publikation 11)**. Insgesamt 45 Lebermetastasen (in der letzten Bildgebung progredient unter Chemotherapie) von 16 Patienten wurden mittels iBT behandelt. Es wurden eine lokale Kontrollrate von 87 %, ein progressionsfreies Überleben von 3,4 Monaten (Range: 1,5–19,6 Monate) und ein medianes Gesamtüberleben von 8,9 Monaten (Range: 3,1–29,3 Monate) erreicht. Drei Major-Komplikationen (drei intrahepatische Abszesse) wurden verzeichnet (32).

Darüber hinaus, das belegen die zwei folgenden Studien, konnte die iBT auch bei der Therapie metastasierter Plattenepithelkarzinome erfolgreich angewendet werden. Bei 7 Patienten mit einem metastasierten Ösophagus-Plattenepithelkarzinom **(Publikation 4)** wurden 21 nicht resektable Metastasen (7 Lungenmetastasen, 9 Lebermetastasen, 4 Lymphknotenmetastasen, 1 Nebennierenmetastasen) mit iBT behandelt: Innerhalb eines medianen Beobachtungszeitraums von 6,3 Monaten entwickelten drei Patienten ein Lokalrezidiv. Daraus resultierte eine lokale Kontrollrate von 85,7 %. Das progressionsfreie Überleben lag bei 3,4 Monaten (Range: 1,3–13 Monate) und das mediane Gesamtüberleben nach iBT bei 13,7 Monaten (Range: 5,6–25,7 Monate).

Eine exzellente lokale Kontrollrate von 97,4 % bei einem Beobachtungszeitraum von 15,2 Monaten konnte bei der Behandlung 38 nicht resektabler Metastasen des Analkarzinoms (7 Patienten) erzielt werden **(Publikation 10)**. Die Metastasen waren in der Leber (n = 28), in der Lunge (n = 9) und in den Lymphknoten (n = 1) lokalisiert. Es zeigten sich ein progressionsfreies Überleben von 3,3 Monaten (Range: 2,5–32,6 Monate) und ein medianes Gesamtüberleben von 25,2 Monaten (Range: 6,5–51,0 Monate). In beiden Arbeiten wurde keine Major-Komplikation verzeichnet.

Die genauere klinische Einordnung der Studien erfolgt im letzten Kapitel dieser Arbeit.

2.2.2 Periinterventionelle Bildführung

In der Übersicht über die bereits publizierten Daten zur bildgeführten iBT kann die Bildführung mittels Computertomografie als Goldstandard angesehen werden. Die Positionierung der die Strahlenquelle aufnehmenden Katheter erfolgt unter CT-Fluoroskopie lediglich an axialen CT-Scans ohne Kontrastmittelverstärkung (33,34). Durch einen verminderten Läsion-zu-Leber-Kontrast ist die Visualisierung speziell kleiner Tumore erschwert (35). Zudem steigt insbesondere der Schwierigkeitsgrad von Punktionen/Interventionen, die eine stärkere Angulation benötigen (subphrenisch gelegene intrahepatische Tumore). Die dadurch häufig verlängerte Interventionsdauer erhöht die Strahlenexposition für Patient und medizinisches Personal. Die exakte Darstellung der Katheterlage im Tumor und ob weitere Katheter benötigt werden, wird erst in einer anschließend durchgeführten kontrastmittelverstärkten CT-Untersuchung beurteilt. Dies kann, wenn auch äußerst selten, repetitive CT-Untersuchungen mit jodhaltigem Kontrastmittel für den Patienten nach sich ziehen, welches das Risiko einer Niereninsuffizienz erhöht (36). Eine geometrisch sinnvolle Anordnung der Katheter im Tumor ist jedoch unerlässlich, um das umliegende Gewebe bestmöglich zu schonen.

Eine weitaus weniger verbreitete, jedoch in unserem Institut der Radiologie und Nuklearmedizin des Universitätsklinikums Magdeburg routinemäßig Einsatz findende bildführende Modalität ist die Magnetresonanztomografie (MRT). Im CT schlecht visualisierbare und ungünstig lokalisierte Lebertumore werden in unserem Institut MRT-gesteuert brachytherapiert **(Publikationen 1, 3–5, 10–11).** Einen wesentlichen Vorteil bietet die Multiplanarität der MRT. Dadurch können die Bildebenen während der Intervention an den gewünschten Zugangsweg angepasst werden. Die Positionierung der Katheter erfolgt anders als im CT mithilfe zwei aufeinander senkrecht stehender Ebenen (angepasste axiale und angepasste koronare Ebene). Auf diese Weise wird auch bei ungünstig lokalisierten Tumoren die Zielansteuerung erleichtert (37–39). Durch die vorhandene koronare Orientierung kann die Intervention problemlos unter freier Atmung erfolgen (40). Eine noch bessere Darstellung, insbesondere kleiner intrahepatischer Tumore sowie der angrenzenden Strukturen (Gefäße oder Gallengänge) wird durch den präinterventionellen Einsatz eines hepatozytenspezifischen Kontrastmittels (Primovist, Bayer, Berlin, Deutschland) erreicht (41). Der vermutlich größte Bonus der MRT-gestützten lokalen Therapie ist die nicht vorhandene Strahlenbelastung für Patient und medizinisches Personal. Ein großer Nachteil der MRT-geführten iBT ist der

limitierte Zugang aufgrund des Platzmangels in den gängigen MRT-Systemen mit Tunnelbauweise (40). Vielmehr eignet sich der Einsatz von offenen MRT-Systemen. In einer Studie von Ricke et al. wurden 224 primäre und sekundäre Lebertumore an einem offenem MRT (1 Tesla) mittels iBT therapiert und eine außerordentliche Effektivität und Sicherheit des Verfahren beschrieben (lokale Kontrolle: 97 %, Major-Komplikationen: 0 %, Minor-Komplikationen: 3 %) (39). Diese Ergebnisse unterstreichen den Stellenwert einer bestmöglichen Visualisierung von Zielläsion und angrenzenden Risikostrukturen, da diese direkt mit dem Behandlungserfolg und der prozeduralen Komplikationsrate korreliert. Aufgrund der begrenzenten Verfügbarkeit offener MRT-Systeme bleibt die MRT-gestützte iBT wenigen spezialisierten Zentren vorbehalten.

Der Ultraschall ist aufgrund seiner geringeren Kosten weltweit deutlich häufiger verfügbar und die am häufigsten eingesetzte bildführende Modalität bei lokalen Ablationen (36). In einer Pilotstudie wurde die Möglichkeit einer Positionierung der Brachytherapiekatheter mittels Ultraschalls untersucht **(Publikation 8)**. 12 Patienten erhielten eine interstitielle Brachytherapie insgesamt 16 abdomineller Tumore (13 primäre und sekundäre Lebertumore; 3 Nierenzellkarzinome). Für die Ablation der 16 Tumore wurden insgesamt 28 Katheter implantiert. 23 der 28 Katheter konnten mittels Ultraschalls positioniert werden. 5 Katheter mussten in Anbetracht eingeschränkter Ultraschallbedingungen komplett mittels CT-Fluoroskopie eingesetzt werden. Insgesamt konnte durch die Zunahme des Ultraschalls die CT-Fluoroskopiezeit pro Eingriff signifikant von 105,5 s (nur CT-Fluoroskopie) auf 14,5 s (Ultraschall-gestützt und CT-Fluoroskopie) reduziert werden ($p = 0{,}006$). Da für die Bestrahlungsplanung ein Schnittbilddatensatz unerlässlich ist, erfolgte postinterventionell ein CT-Scan. Keine Major- oder Minor-Komplikation wurde verzeichnet. Im Vergleich zum CT wurde eine bessere Visualisierung der Läsionen suggeriert, wenngleich der Unterschied nicht signifikant war. Wie aus bereits publizierten Studien zur Ultraschall-gestützten Radiofrequenzablation bekannt erwies sich eine ungünstige Lokalisation der Zielläsion als Restriktion des Ultraschalls. Die häufig beschriebene Limitation des Ultraschalls durch die bei der thermischen Ablation entstehenden Gasbläschen spielt bei der iBT keine Rolle.

2.2.3 Periinterventionelles Management

2.2.3.1 Präinterventionelle Vorbereitung

Zur präziesen Planung der bildgeführten interstitiellen Brachytherapie wird vorab eine Magnetresonanztomografie (MRT) der Leber mit dem hepatozytenspezifischen Kontrastmittel Primovist (Bayer Schering, Berlin, Deutschland) durchgeführt. Aufgrund der im Vergleich zum CT erhöhten Sensitivität der Untersuchung (41) wird diese als Grundlage zur Definition von Größe und Anzahl der Tumore herangezogen. Dadurch können auch die im CT schlechter visualisierbaren Tumore detektiert und tumorumschließend behandelt werden. Eine vorab durchgeführte Computertomografie von Thorax und Abdomen dient dem Ausschluss eines diffusen systemischen Progresses, da solch einer eine Kontraindikation für die lokale Therapie darstellt. Weitere Vorrausetzungen für die Durchführung der bildgeführten Brachytherapie sind der oligometastatische Charakter der Erkrankung, ein ECOG-Perfomancestatus < 2 (ECOG = East Coast Oncology Group) sowie adäquate Gerinnungsparameter des Patienten (Thrombozyten > 50 000/nl, PTZ/Quick < 50 %, partielle Thromboplastinzeit [PTT] < 50 s) (42). Die Entscheidung zur lokalen Therapie wird in einer interdisziplinären Tumorkonferenz gefällt.

2.2.3.2 Follow-up

Neben der routinemäßigen laborchemischen Kontrolle werden zur bildmorphologischen Verlaufskontrolle alle drei Monate eine kontrastmittelgestützte MRT-Untersuchung des Oberbauchs (Primovist) und eine CT-Untersuchung Thorax/Abdomen (Imeron) durchgeführt. Durch die verminderte Aufnahme des hepatozytenspezifischen Kontrastmittels in postradiogen verändertem Leberparenchym kann in T1-gewichteten Sequenzen der MRT zusätzlich zur Tumorkontrolle das Ausmaß einer Leberfunktionseinschränkung des umliegenden Gewebes visualisiert werden. Der damit entstandene hypointense Saum um den therapierten Tumor fungiert als Surrogat für den Bestrahlungseffekt. Eine Schwellenwertdosis – als jene Dosis, die einen (meistens reversiblen) Funktionsverlust der Hepatozyten bewirkt – ist in der Literatur mit 9,4 Gy angegeben. Im weiteren Verlauf zeigt sich bedingt durch die Regenerationsfähigkeit der Leber eine Normalisierung des umliegenden Gewebes. Mithilfe weiterer Sequenzen, wie der T2-gewichteten Sequenzen zur Detektion von Tumorödem und der DWI zur Visualisierung vitalen Tumorgewebes, werden lokale Tumorprogressionen im Ablationsareal beurteilt.

2.3 Vorteile der bildgeführten interstitiellen Brachytherapie

Im Gegensatz zur normofrequenten Bestrahlungsmethode können mit der hypofraktionierten Strahlentherapie, wie der bildgesteuerten interstitiellen Brachytherapie (Afterloading-Technik), aber auch der SBRT, gezielt höhere lokale Dosen am Tumor appliziert werden. Der hohe zytotoxische Effekt ermöglicht dadurch auch die Bestrahlung von Tumoren, die für die konventionelle Bestrahlungsmethode (Normofraktionierung) als strahlungsresistent galten. So konnte in einer retrospektiven Analyse die hohe Effektivität der iBT bei der Behandlung von Nierenzellkarzinommetastasen der Leber aufgezeigt werden **(Publikation 1).** 54 nicht resektable Metastasen von 14 Patienten konnten mit einer exzellenten lokalen Kontrollrate von 92,6 % therapiert werden (medianer Beobachtungszeitraum: 10,2 Monate, Range: 2,4–73,6 Monate). Es wurden ein progressionsfreies Überleben nach iBT von 3,4 Monaten (Range: 1,0–27,8 Monate) sowie ein medianes Gesamtüberleben von 51,2 Monaten (Range: 10,2–81,5) erreicht. In einer Arbeit von Franzese et al. konnte eine vergleichbar gute lokale Kontrollrate für die SBRT veranschaulicht werden: Bei 58 Patienten mit 73 Metastasen in verschiedenen Organen wurde eine lokale Kontrollrate von 90,2 % nach 18 Monaten beschrieben (43).

Die hohe biologische Wirksamkeit der iBT erwies sich auch in der Behandlung der üblicherweise als strahlenresistent geltenden gastrointestinalen Stromatumore (GIST) als erfolgsversprechend. Mit einer medianen tumorumschließenden Dosis von 15 Gy wurde bei 40 Imatinib-refraktären Metastasen (30 Lebermetastasen, 10 peritoneale Metastasen) von 10 Patienten eine lokale Kontrolle von 97,5 % (medianer Beobachtungszeitraum: 25 Monate) verzeichnet **(Publikation 3)**.

Zu erwähnen ist, dass es sich bei der tumorumschließenden Zieldosis nach iBT um die geringste Dosis am Tumor handelt. Anders als bei der SBRT wird mittels iBT eine außerordentliche Heterogenität der Strahlendosis im Tumor erreicht. Die Dosis im Zielvolumen selbst, insbesondere zwischen den einliegenden Bestrahlungskathetern, ist exorbitant hoch und erhöht damit nochmals den zytotoxischen Effekt (33).

Die SBRT gilt als sicheres und effektives, jedoch dosishomogenes Verfahren mit Einzeldosen von etwa 10–20 Gy, üblicherweise appliziert in 3–5 Fraktionen (44,45). Da es sich bei der Stereotaxie um eine Bestrahlung von außen nach innen handelt, wird ein mehrfacher Einsatz durch die kumulative Dosis auf das gesunde umliegende Gewebe erschwert.

Die interstitielle Brachytherapie mit Bestrahlung von innen nach außen bietet durch eine höhere Einzelfraktion mit einem steilen Dosisgradienten die bestmögliche Schonung des umliegenden Gewebes. In der Regel handelt es sich bei der iBT um ein sogenanntes einzeitiges Vorgehen.

Im Gegensatz zur SBRT ist die interstitielle Brachytherapie unabhängig von Atemverschiebungen: Aufgrund der kutanen Fixierung der Bestrahlungskatheter und der damit gesicherten Lage der intrakorporalen Katheterspitze im Tumor bleiben Atemverschiebungen während der Bestrahlung ohne Einfluss. Dennoch sollte bei vergleichbaren Ergebnissen der lokalen Kontrollraten im Einzelfall zwischen Stereotaxie und interstitieller Brachytherapie entschieden werden. Insbesondere bei solitären Läsionen sollte die höhere Invasivität der interstitiellen Brachytherapie bei der Entscheidung berücksichtigt werden.

Im Vergleich zu thermischen Ablationsverfahren gilt für die interstitielle Brachytherapie keine Limitation durch Kühlungseffekte. Während außerdem bei den thermischen Ablationsverfahren, wie der Radiofrequenzablation, das Ablationsareal vom Applikatordesign bestimmt wird, kann die Bestrahlungsgeometrie bei der iBT über die Haltedauer der Hochdosis-Iridium^{192}-Quelle an verschiedenen Lokalisationen im Bestrahlungskatheter der Tumorgeometrie angepasst werden. Daraus resultieren eine flexible, ubiquitäre Anwendung des Verfahrens (auch extrahepatisch und extrapulmonal) und die Möglichkeit, auch große Tumore > 10 cm mittels interstitieller Brachytherapie zu behandeln (30,46).

So konnte eine retrospektive Analyse **(Publikation 2)** den sicheren und effektiven Einsatz der perkutanen CT- gesteuerten interstitiellen Brachytherapie am Pankreas aufzeigen. Bei 13 Patienten mit nicht resektablen primären und sekundären Pankreastumoren (8 Pankreasmetastasen und 5 primäre Pankreastumore, davon 3 Lokalrezidive nach Pankreasresektion) wurde bei einer medianen tumorumschließenden Dosis von 15,3 Gy und einem medianen Beobachtungszeitraum von 6,7 Monaten eine lokale Kontrolle von 92,3 % erreicht. Alle Tumore waren im Pankreaskorpus oder Pankreasschwanz lokalisiert. Der mediane Durchmesser der Tumore lag bei 3 cm (Range: 1–6,5 cm). Ein Patient entwickelte eine akute Pankreatitis in milder Ausprägung, die nach einer Woche selbstlimitierend war (Komplikation Grad II CTCAE). Komplikationen Grad III+ wurden nicht beobachtet. Die Strahlenexposition von angrenzenden Risiko-

organen wie Magen und Darm blieb unter der jeweiligen organspezifischen Dosisgrenze. In den dreimonatigen Verlaufskontrollen mittels CT und MRT gab es keine Zeichen von Spätkomplikationen, wie Pankreatitis oder Gallengangsstrikturen.

Deutlich höhere Komplikationsraten lassen sich sowohl für die perkutane als auch für die intraoperative Anwendung thermischer Ablationsverfahren am Pankreas verzeichnen. In einer Arbeit von Rossi et. al wurde für die Ultraschall-gestützte Radiofrequenzablation am Pankreas eine Major-Komplikationsrate von 30 % beschrieben (47). Hervorzuheben ist zudem die deutlich kleinere Tumorgröße (mittlere Durchmesser 1,6 cm, Range: 0,9–2,9 cm) als in unserer Studie zur CT-gesteuerten interstitiellen Brachytherapie von Pankreastumoren. Vergleichbare Komplikationsraten (24–28 %) zeigt die Anwendung thermischer Ablationen im operativen Setting (48,49).

In einer weiteren Arbeit zur Evaluierung der extrahepatischen und extrapulmonalen Anwendung der bildgeführten interstitiellen Brachytherapie wurden 47 retroperitoneale Lymphknoten (an der Mesenterialwurzel, am Truncus coelicus und paraaortal) behandelt **(Publikation 12)**. Es zeigte sich eine lokale Kontrollrate von 95,7 % (medianer Beobachtungszeitraum: 9,6 Monate, Range: 2,9–39 Monate). Ein Patient (4,17 %) entwickelte postinterventionell einen retroperitonealen Abszess mit begleitender Spondylodiszitis, welcher im weiteren Verlauf operativ behandelt werden musste (CTCAE Komplikation Grad III +). Im Gegensatz zeigt eine Studie von Gao et al. zur CT-gesteuerten Radiofrequenzablation retroperitonealer Lymphknotenmetastasen an 19 Patienten eine lokale Kontrollrate von 41,7 % nach 10 Monaten (50). Während dieselbe Arbeit eine Komplikationsrate von 0 % aufweist, verzeichnen Machi et al. nach Ultraschall-gesteuerter Radiofrequenzablation retroperitonealer und pelviner Lymphknoten eine postinterventionelle Komplikationsrate von 27,5 % (3 von 7 Patienten) und eine lokale Kontrollrate von 71,4 % (51).

Wie bereits oben erwähnt unterliegt die Anwendung der bildgeführten interstitiellen Brachytherapie keiner Größenlimitation. In einer Studie von Mohnike et al. konnte bei 83 Patienten mit hepatozellulärem Karzinom mit insgesamt 126 Tumorherden und einer medianen Tumorgröße von 5,2 cm (Range: 1–15 cm) bei einer tumorumschließenden Dosis von 20 Gy eine Kontrollrate von 90 % nach 12 Monaten erzielt werden (52). Diese Ergebnisse lassen sich in einer weiteren Arbeit von Collettini et al. gut reproduzieren (35 HCCs > 5 cm, mittlere Tumorgröße: 7,1 cm, lokale Kontrolle: > 90 % nach 12,6 Monaten Beobachtungszeitraum) (53). Dennoch scheint auch für die interstitielle

Brachytherapie die Behandlung großer Tumore aus strahlenbiologischer Sicht eine größere Herausforderung darzustellen. Dosisexpositionsanalysen von Lokalrezidiven konnten zeigen, dass nicht nur das Erreichen der tumorumschließenden Dosis essenziell ist, sondern auch die ausreichende Abdeckung eines Sicherheitssaums, in dem sich Mikrometastasen absiedeln (54). Für Metastasen kolorektaler Karzinome zeigte eine Dosisexpositionsanalyse von 34 Lokalrezidiven, dass 90 % der Metastasen hätten vermieden werden können, wenn ein Sicherheitssaum von 2 cm um die behandelte Läsion mit 15 Gy bestrahlt worden wäre. Dies wiederum würde eine tumorumschließende Dosis von 25 Gy bedeuten (55). Das Ergebnis steht in Einklang mit einer Dosisfindungsanalyse von Ricke et al. zur Bestrahlung kolorektaler Lebermetastasen: In dieser prospektiv randomisierten Studie an insgesamt 73 Patienten mit 199 irresektablen Metastasen kolorektaler Karzinome zeigte sich nach CT-gesteuerter interstitieller Brachytherapie eine lokale Kontrollrate von 97 % im Fall einer tumorumschließenden Dosis mit 25 Gy. Wurden die Tumore lediglich mit 20 oder 15 Gy tumorumschließend behandelt, sank die lokale Kontrollrate auf 78 und 65 % (56). Insbesondere bei größeren Tumoren mit häufiger unregelmäßiger Randbegrenzung, die an strahlensensible Risikoorgane wie Magen und Darm grenzen, ist die Applikation von 25 Gy tumorumschließend nicht immer möglich. So könnte dies einen Erklärungsansatz für die von Collettini et al. veröffentlichten Ergebnisse bieten, denen zufolge die lokale Kontrolle bei Tumoren mit einem Durchmesser > 4 cm nach 12 und 24 Monaten auf 65,8 und 58,5 % sinkt, während sie bei Tumoren mit einem Durchmesser < 4 cm bei 94 und 86,8 % liegt. Jedenfalls ist festzuhalten, dass die interstitielle Brachytherapie durch die Einhaltung der Dosisgrenzwerte umliegender Risikostrukturen limitiert wird. Aus diesem Grund wurde untersucht, inwiefern ein perkutanes Distendieren des Risikoorgans vom zu bestrahlenden Zielvolumen möglich ist. Ziel der Studie war es, die Exposition des Risikoorgans durch einen zwischen Zielläsion und Risikoorgan gesetzten Ballonkatheter zu reduzieren **(Publikation 7)**. Hierfür erhielt ein Kollektiv von 31 Patienten mit subkapsulären hepatischen Tumoren (29 im Lebersegment II/III mit Nähe zum Magen und 2 rechtshepatische Tumore mit Nähe zum Kolon) nach Anlage der Bestrahlungskatheter einen oder zwei Ballonkatheter, um den Abstand zwischen Risikoorgan und Zielvolumen zu erhöhen. Anschließend erfolgte eine interstitielle Brachytherapie mit einer tumorumschließenden Dosis zwischen 15 und 20 Gy, abhängig von der Tumorentität.

Mit Ballonkatheter konnte die Punktdosis (D1cc in Gy/cm³) am Risikoorgan signifikant reduziert werden (median D1cc 12,6 Gy vs. 16 Gy ohne Ballonkatheter). Als Vergleich wurde eine berechnete virtuelle Punktdosis am Risikoorgan ohne Ballonkatheter herangezogen. Die virtuelle Position des Risikoorgans wurde anhand der CT-Fluoroskopie vor Einbringen des Ballonkatheters festgemacht. In der Analyse zeigten sich keine auf das Einführen der Ballonkatheter zurückzuführenden Komplikationen. Der Einsatz von Ballonkathetern bietet eine sichere Methode zur Bestrahlung an Risikoorgane angrenzender Tumore (häufig eine Herausforderung von großen Tumoren). Ballonkatheter erlauben eine effektive, hohe tumorumschließende Dosis an der Zielläsion unter gleichzeitiger Schonung angrenzender Risikoorgane und reduzieren dadurch die Wahrscheinlichkeit von Lokalrezidiven.

Ein weiterer wesentlicher Vorteil der iBT gegenüber der thermischen Ablation liegt in der Möglichkeit, Tumore in der Nähe hitzevulnerabler Strukturen, wie Gallengänge und Gallenblase, zu therapieren. Dies gilt insbesondere für die Behandlung zentraler Tumore am Leberhilus, der unabhängig von der Tumorentität auch für die chirurgische Resektion eine klinische Herausforderung darstellt. Der Einsatz thermischer Ablationen am Leberhilus ist aufgrund der Kühlungseffekte angrenzender Gefäße mit erhöhten Lokalrezidivraten vergesellschaftet. Zudem besteht nach thermischer Ablation ein erhöhtes Risiko für Gallengangskomplikationen. Thermische Ablationen haben sich demnach bei der Behandlung zentraler Tumore als ungeeignet erwiesen (57). Damit nimmt die Bestrahlungstherapie in der Behandlung zentraler Lebertumore eine wichtige Rolle ein: So konnten Collettini et al. anhand einer retrospektiven Analyse von 34 Metastasen mit einem Abstand von < 5 mm zum Leberhilus zeigen, dass die CT-gesteuerte interstitielle Brachytherapie bei einer Komplikationsrate von 2,63 % (ein Patient mit biliodigestiver Anastomose entwickelte einen Abszess) und einer lokalen Kontrolle von 88,2 % eine sichere und effektive Behandlungsmethode zentraler Lebertumore darstellt. Ein vergleichbar gutes Ergebnis konnte in einer weiteren Arbeit zur iBT von zentralen Tumoren gezeigt werden: Bei 20 zentralen Leberläsionen, die für eine RFA ungeeignet waren, konnte mittels iBT eine lokale Kontrollrate von 93 % nach 12 Monaten erreicht werden (58). Damit scheint die bildgesteuerte interstitielle Brachytherapie eine vielversprechende Methode jenseits der Indikation thermischer Ablationsverfahren zu sein.

Die aufgezeigten guten Ergebnisse hinsichtlich Sicherheit und Effektivität der iBT sowie der hohe zytotoxische Effekt führten zu der Annahme, dass die iBT eine mögliche

Alternative zur transarteriellen Chemoembolisation (TACE) im Bridging hepatozellulärer Karzinome vor Lebertransplantation sein kann. Zum klinischen Verständnis muss erwähnt sein, dass die Erfolgsrate bzw. das Überleben nach Lebertransplantation von der Aggressivität (Nekroserate) der zuvor behandelten Tumore abhängt: Patienten mit kompletter Response vor Lebertransplantation haben ein signifikant höheres 5-Jahres-Überleben als Patienten mit partieller Response (87 vs. 62 %; p = 0,02) (59).

Der hohe zytotoxische Effekt der interstitiellen Brachytherapie führt zur gewünschten hohen Nekroserate des behandelten Tumors. So zeigten Denecke et al. in einer Matched-Pair-Analyse eine signifikant höhere Nekroserate nach interstitieller Brachytherapie als nach TACE (63 [± 10] vs. 22 [± 7] %; p = 0,002) (60). Weiter konnte eine randomisierte Phase-2-Studie von Mohnike et al. bei 77 Patienten mit HCC eine signifikant verlängerte progressionsfreie Zeit nach interstitieller Brachytherapie (n = 37) als nach TACE (n = 40) zeigen (12,8 vs. 5,7 Monate). Erwähnenswert ist zudem, dass in der Studie von Mohnike et al. aufgrund technischer Limitationen 14 der 40 Patienten im TACE-Arm ein Crossover zur Brachytherapie benötigten, um eine lokale Kontrolle des Tumors zu erlangen (61). Mit diesen Ergebnissen erweist sich die interstitielle Brachytherapie als minimalinvasive, aber dennoch aggressive Therapie mit hoher biologischer Wirksamkeit und höherer Nekroserate als nach TACE. In prospektiven Studien sollte demnach der Einsatz der iBT in der Bridging-Situation hepatozellulärer Karzinome validiert werden.

2.4 Komplikationen lokal ablativer Verfahren

Prinzipiell können bei bildgesteuerten lokal ablativen Verfahren zwei Gruppen von Komplikationen unterschieden werden:

1. Komplikationen der Punktion während der Sonden- oder Katheterpositionierung (thermische Ablation oder iBT). Hierzu zählen Infektionen, Blutungen, Verletzungen umliegender Strukturen sowie die Tumorzellverschleppung.
2. Komplikationen des Ablationsmechanismus. Hierzu gehören Hitzeschäden bei thermischer Ablation und radiogen induzierte Schädigungen bei der iBT.

Daten von größeren Patientenkollektiven zu Komplikationsraten nach lokal ablativen Tumortherapien lagen lange Zeit lediglich für thermische Ablationsverfahren vor. So berichten Livraghi et al. in einer multizentrischen Studie eine Major-Komplikationsrate von 2,2 % nach Radiofrequenzablation von 3554 Tumorläsionen. Am häufigsten waren

peritoneale Blutungen, Stichkanalmetastasen, intrahepatische Abszesse sowie Darmperforationen (62). In einer Metaanalyse von Bertot et al. liegt die Major-Komplikationsrate nach 9531 Radiofrequenzablationen bei 4,1 % (63). Das Mortalitätsrisiko nach Radiofrequenzablation beläuft sich auf 0,3 % (62). Die Ergebnisse unterstreichen, insbesondere im Vergleich zu der in der Literatur beschriebenen Morbiditäts- und Mortalitätsrate nach chirurgischer Resektion (15–30 % und 5 %) den schonenden und sicheren Charakter der thermischen Ablation (64,65).

2.4.1 Komplikationen der bildgeführten interstitiellen Brachytherapie

2.4.1.1 Punktionsbedingte Komplikationen

In einer Studie von Mohnike et al. wurden für die iBT ähnlich geringe Komplikationsraten beschrieben wie für die Radiofrequenzablation. Bei insgesamt 192 Patienten mit 343 durchgeführten CT- oder MRT-gestützten Brachytherapien der Leber unter Verwendung von 1275 Bestrahlungskathetern wurde eine Major-Komplikationsrate von 4,1 % beobachtet (66). Eingeschlossen wurden verschiedene Tumorentitäten (kolorektales Karzinom: 43,8 %, hepatozelluläres Karzinom: 26 %, cholangiozelluläres Karzinom: 8,3 %, Mammakarzinom: 6,7 %, Bronchialkarzinom: 4,2 %, Andere: 10,9 %).

Während der Positionierung der (die Strahlenquelle tragenden) Katheter zeigte sich eine punktionsbedingte Major-Komplikationsrate (Grad 3/4 der CTCAE-Klassifikation) von 2,9 %. Hierzu zählen 5 Blutungen (1,36 %), die bemerkenswerterweise ausschließlich in Patienten mit einem HCC auftraten. Das Vorhandensein einer Leberzirrhose wurde als signifikanter Risikofaktor einer Blutungskomplikation verzeichnet. Zudem zeigten sich 4 intrahepatische Abszesse und eine akute obstruktive Cholangitis. Weitere Studien, die sich ausschließlich mit der Komplikationsrate nach bildgeführter iBT befassen, existieren nicht. Dennoch kann dieses Ergebnis auch durch unsere Arbeiten sehr gut reproduziert werden. In unseren Sicherheitsanalysen der iBT bei unterschiedlichen Entitäten (Nierenzellkarzinom, Analkarzinom, Ösophaguskarzinom, Magenkarzinom, Pankreaskarzinom und gastrointestinale Stromatumore) wurden kumulativ 118 CT- oder MRT-gestützte Brachytherapien der Leber durchgeführt (30,32,42,46,67,68). Insgesamt zeigten sich 6 Major-Komplikationen (5 %). Im Einzelnen handelte es sich um eine hepatische Blutung, die angiografisch erfolgreich embolisiert werden konnte, einen drainagewürdigen Pneumothorax nach iBT einer subkapsulären Metastase im Lebersegment VIII sowie um vier antibiotisch und mittels Drai-

nage behandelte intrahepatische Abszesse. Drei der vier Patienten mit postinterventionellem Abszess hatten eine biliodigestive Anastomose nach Pankreasresektion (bei Pankreaskarzinom). Eine biliodigestive Anastomose stellt aufgrund einer möglichen Keimbesiedlung der intrahepatischen Gallengänge ein erhöhtes Risiko zur Ausbildung von Abszessen dar.

Ein weiteres punktionsbedingtes Risiko während der iBT ist die Verschleppung von Tumorzellen. Stichkanalmetastasen entstehen durch eine verminderte Zell-Zell-Adhäsion in Tumorzellgewebe. Dadurch können bei Manipulation am Tumorgewebe Zellen migrieren und an einem anderem Ort eine neue Metastase ausbilden (69). Die meisten diesbezüglichen Daten beziehen sich auf Stichkanalmetastasen nach Biopsien: Die vermutlich größte Studienpopulation bietet die Untersuchung von Smith et al. Bei 63 108 abdominellen Biopsien unterschiedlicher Tumorentitäten wurde eine Stichkanalmetastasenrate von 0,005–0,009 % beschrieben (70). Betrachtet man lediglich Stichkanalmetastasen nach Biopsie eines hepatozellulären Karzinoms, werden in der Literatur Raten von 1,6–2,7 % beschrieben (71–73).

Daten zum Risiko einer Stichkanalmetastase nach lokalen thermischen Ablationen existieren hauptsächlich für das hepatozelluläre Karzinom. So verzeichnete eine Metaanalyse von Stigliano et al. nach Radiofrequenzablation hepatozellulären Karzinome das Auftreten von Stichkanalmetastasen in 0,61 %. Wurde die RFA mit einer vorherigen Biopsie kombiniert, beläuft sich die Komplikationsrate auf 0,95 % (71). Grund für die niedrigere Rate in der Gruppe „RFA ohne Biopsie“ ist vermutlich die in dieser Gruppe teilweise angewandte zusätzliche Ablation des Stichkanals (Track Ablation). Zu ähnlichen Ergebnissen kommen weitere Studien, in denen sich das Risiko einer Stichkanalmetastase nach RFA hepatozellulärer Karzinome auf 0,5–1,2 % beläuft (74,75). Zu erwähnen ist, dass die meisten Studien lediglich auf extrahepatische Stichkanalmetastasen untersuchten und mögliche intrahepatische Metastasen nicht berücksichtigten. Doch können sich insbesondere bei längerem intrahepatischen Verlauf Tumorzellen beim Rückzug der Nadel bereits intrahepatisch ansiedeln und erst gar nicht nach extrahepatisch gelangen. Demnach würde die Aufzeichnung lediglich extrahepatischer Stichkanalmetastasen das „echte Risiko“ von Stichkanalmetastasen unterschätzen.

In unserer retrospektiven Analyse zur Häufigkeit von Stichkanalmetastasen wurden daher nach 233 CT- oder MRT-gesteuerten Brachytherapien hepatozellulärer Karzinome sowohl extrahepatische als auch intrahepatische Stichkanalmetastasen aufgezeichnet **(Publikation 9)**. Insgesamt wurden 588 Bestrahlungskatheter positioniert. Eine Stichkanalbestrahlung analog zur Track Ablation nach thermischer Ablation fand nicht statt. 98 der 100 Patienten hatten eine Leberzirrhose. Eine bildgebende Verlaufskontrolle erfolgte alle 3 Monate mittels CT und/oder MRT der Leber. Der Mindestbeobachtungszeitraum belief sich auf 6 Monate. Zur Beurteilung einer Stichkanalmetastase wurden folgende Kriterien beachtet:

1. Zeitliche Kausalität: Die Metastase sollte in einem Zeitraum von zwei Jahren nach durchgeführter iBT aufgetreten sein.
2. Kausalität bezüglich der Lokalisation: Jede neu aufgetretene Metastase in einem Radius von 1 cm um die frühere Katheterposition wurde als hochgradig verdächtig definiert.

Zur exakten Beurteilung wurde im weiteren Verlauf eine Fusion der Nachsorge-Bildgebung (mit neu detektierter Metastase) und der Bestrahlungsbilder (mit Katheterposition) durchgeführt (Software: Amira Version 3.1). Bei einem medianen Beobachtungszeitraum von 15,7 Monaten (Range: 6–70,2 Monate) wurden bei 588 eingesetzten Bestrahlungskathetern 9 Stichkanalmetastasen (1,5 %) beobachtet, in 7 Fällen intrahepatische (1,2 %) und in 2 Fällen extrahepatische (0,3 %). Das mediane Zeitintervall bis zum Auftreten einer Stichkanalmetastase belief sich auf 5,5 Monate (Range: 4,8–6,2). Bei einer medianen Katheteranzahl von 2,6 pro Tumorläsion ergab sich pro Tumorläsion ein Risiko von 3,9 % (3,0 % intrahepatisch, 0,9 % extrahepatisch). Hinzuzufügen ist, dass 8 der 9 Stichkanalmetastasen in einer weiteren Sitzung mittels iBT behandelt werden konnten. Ein Patient erhielt bei gleichzeitigem systemischen Progress eine Systemtherapie. Analysen zu möglichen Einflussgrößen, wie Geschlecht, Alter, Differenzierungsgrad des Tumors, Vorhandensein einer Tumorpseudokapsel, Ätiologie der Leberzirrhose, In-situ-Katheterlänge, Durchstehen der Zielläsion, Ablationsdosis und gleichzeitige systemische Behandlung, ergaben jeweils keinen signifikanten Einfluss auf die Entstehung von Stichkanalmetastasen.

Lediglich die Tumorgröße der bestrahlten Läsion scheint einen Einfluss auf die Ausbildung von Stichkanalmetastasen zu haben. So wurden Stichkanalmetastasen häufiger nach Ablation kleiner Tumore beobachtet ($p = 0,09$) (76). Grund hier ist vermutlich der

erhöhte Schwierigkeitsgrad bei kleinen Läsionen und die möglicherweise deswegen vermehrte Manipulation am Tumor, um eine exakte Position der Katheter zu erreichen. Eine ähnliche Hypothese erlaubt die Studie von Rogits et al. zu Stichkanalmetastasen nach bildgeführter iBT kolorektaler Lebermetastasen, die ein erhöhtes Auftreten von Stichkanalmetastasen nach MRT-gestützter Brachytherapie im Vergleich zu CT-gestützter Brachytherapie verzeichnet (p = 0,03). In diesem Zusammenhang muss erwähnt werden, dass hauptsächlich kleine, im CT nicht visualisierbare Läsionen MRT-gestützt therapiert werden. Insgesamt wurden in der Studie von Rogits et al. bei 1107 hepatisch eingesetzten Bestrahlungskathetern 11 Stichkanalmetastasen beobachtet (1 % pro Katheter) (77). In einer weiteren Analyse von Denecke et al. wurde in einer Studie zur Evaluation eines möglichen Einsatzes der iBT in der Bridging-Situation vor Lebertransplantation keine Stichkanalmetastase nach iBT beobachtet, wenngleich diese Untersuchung an einem deutlich kleineren Patientenkollektiv erfolgte (60). Diese sehr geringe Rate an Stichkanalmetastasen (0,2 % extrahepatische Stichkanalmetastasen) ist ein weiteres Argument für den Einsatz der iBT als Ablationsverfahren in der Bridging-Situation hepatozellulärer Karzinome. Die komplette Vermeidung von Stichkanalmetastasen nach iBT erhofft man sich aktuell durch die zusätzliche Bestrahlung des Stichkanals mittels 10 Gy analog zur Track Ablation nach Radiofrequenzablation. Die Track Ablation konnte die Inzidenz von Stichkanalmetastasen nach RFA nachweislich senken (71,78,79).

2.4.1.2 Strahlenbedingte Komplikationen

Strahleninduzierte Nebenwirkungen können sowohl die Zielorgane selbst als auch benachbarte Strukturen/Organe betreffen. Als das am häufigsten von Metastasen befallene Organ steht die Leber im Mittelpunkt der bildgeführten interstitiellen Brachytherapie. Die Anwendung der Radiotherapie ist aufgrund der Radiotoxizität des umliegenden gesunden Lebergewebes begrenzt. Strahleninduzierte Leberparenchymschädigungen äußern sich klinisch unabhängig vom Bestrahlungsformat in einer sogenannten Radiation Induced Liver Disease (RILD) (80). Die klinische und laborchemische Manifestation ist unspezifisch: In der Regel leiden Patienten unter Fatigue, Bauchschmerzen, Aszites, Hepatomegalie, Hyperbilirubinämie (> 2 mg/dl). Typischerweise tritt die RILD 4–8 Wochen nach der Bestrahlungstherapie auf, kann aber auch als Früh- (2 Wochen) oder Spätkomplikation (7 Monate) vorkommen (81). Ob die Strahlentoleranz der Leber überschritten wird und es zur Ausbildung einer RILD kommt, hängt von

mehreren Faktoren ab: applizierte Dosis, Ausmaß des geschädigten Lebervolumens sowie funktionelle Parenchymreserve. In der Literatur werden unterschiedliche Angaben zur Strahlentoleranz der Leber gemacht. Eine mittlere Dosis bis 30 Gy nach normofraktionierter Ganzleberbestrahlung mit jeweils 2 Gy wird bei normaler Leberfunktion als Schwellenwert angesehen (82). Für die hypofraktionierte Bestrahlungstherapie ergibt sich dadurch umgerechnet (über das linearquadratische Modell) ein Schwellenwert von etwa 11,25 Gy.

In einer Studie zur Toleranzdosis der Leber nach iBT konnten Seidenticker et al. anhand postaktinischer Leberparenchymveränderungen im MRT mit hepatozytenspezifischen Kontrastmittel zeigen, dass die Funktionseinschränkung sechs Wochen nach iBT einen Peak erreicht. Funktionsgestörte Hepatozyten zeigen sich durch eine reduzierte Aufnahme des hepatozytenspezifischen Kontrastmittels in der T1-gewichteten Spätphase nach 20 Minuten. Mittels Dosis-Volumen-Histogrammen ermittelten Seidensticker et al. eine Strahlentoleranzdosis der Leber nach iBT von im Median 9,4 Gy. Nach 9 und 12 Wochen zeigte sich das funktionseingeschränkte Areal im MRT rückläufig (83), vermutlich zurückzuführen auf Regenerationsmechanismen des Leberparenchyms.

Aufgrund der Möglichkeit einer dreidimensionalen Bestrahlungsplanung kann der einhergehende Funktionsausfall des umliegenden Leberparenchyms nach iBT annäherungsweise vorausgesagt werden. Dennoch muss auch eine interindividuelle Variabilität unbedingt beachtet werden. Patienten mit gestörter Leberfunktion (bspw. nach Chemotherapie oder bei reduziertem Lebervolumen) haben eine geringere Strahlentoleranz und sind damit anfälliger für die Entwicklung einer RILD (84). In der Praxis werden deswegen bei der Anwendung der iBT bereits 5 Gy als Schwellenwert für radiogen induzierte Parenchymschädigungen definiert. Die Anzahl der in einer Sitzung mittels iBT therapierbaren Lebermetastasen wird limitiert, wenn 66 % der Leber mit 5 Gy exponiert werden (33). In Falle einer notwendigen Überschreitung dieser Lebergesamtdosis (z. B. bei einer Debulking-Ablation sehr großer Lebertumore) ist eine medikamentöse Radioprotektion vorgesehen. Eine prospektive Studie von Seidensticker et al. konnte für die Kombinationstherapie aus Heparin, Pentoxifyllin und Urodeoxycholsäure einen positiven Einfluss zur Protektion der Leber nach einer Bestrahlungstherapie zeigen (85).

In den Sicherheitsanalysen der iBT bei unterschiedlichen Entitäten (30,32,42,46,67,68) wurde unter Beachtung des beschriebenen Sicherheitskonzepts (maximale Exposition von 66 % der Leber mit 5 Gy) bei kumulativ 118 bildgeführten Brachytherapien der Leber keine RILD beobachtet. In der dezidierten Analyse von Mohnike et al. zu den Komplikationen nach iBT trat die RILD, wenn auch nicht in klassischer Form, bei 1 von 192 Patienten (0,05 %) auf (66).

Auch existieren erste Daten zur Auswirkung der iBT auf die Nierenfunktion. Es scheint, als würde die kontralaterale Niere Funktionseinschränkungen des bestrahlten Nierenparenchyms, ähnlich wie vom Leberparenchym bekannt, durch eine funktionelle Hypertrophieinduktion kompensieren können. Hierzu untersuchten Damm et al. in einer prospektiven Analyse an 16 Patienten Nierenfunktionsverluste innerhalb von 12 Monaten nach iBT primärer und sekundärer Nierentumore. Bei einer medianen Strahlendosis (CTV/D100) von 16,37 ± 2,18 Gy wurde eine lokale Kontrollrate von 85 % erreicht. Laborchemisch und mittels Nierenszintigrafie wurde keine signifikante Verschlechterung der glomerulären Filtrationsrate erfasst. Interessanterweise zeigte sich nierenszintigrafisch postinterventionell eine kompensatorische Steigerung der tubulären Extraktionsrate (TER) der kontralateralen Niere, während für die behandelte Niere eine reduzierte tubuläre Extraktionsrate gemessen wurde. Ein Patient mit bereits vorbekannter Niereninsuffizienz Grad IV und mittels Radiofrequenzablation vorbehandelter Niere entwickelte eine Dialysepflicht (86).

Insgesamt ist festzustellen, dass strahleninduzierte Funktionseinschränkungen des behandelten Zielorgans wie Leber und Niere während der iBT eine eher untergeordnete Rolle spielen. Dies unterstreicht den schonenden Charakter der iBT auf das tumorumliegende Gewebe.

Weitere strahleninduzierte Komplikationen können aufgrund der anatomischen Lageverhältnisse die umliegenden Strukturen und Organe betreffen. Angesichts der am häufigsten hepatisch angewandten iBT stehen hier insbesondere Gallenblase, Magen und Darm im Fokus. Entscheidend ist die Einhaltung der organspezifischen Dosisgrenzwerte, die in Studien ermittelt wurde. So verzeichneten Streitparth et al. eine Grenzdosis für gastrische Toxizitäten (Gastritis, Übelkeit, Erbrechen) von 11 Gy und für gastrische bzw. duodenale Ulzerationen von 15,5 Gy (87). Zu einem ähnlichen Ergebnis kommen Mohnike et al. in ihrer Analyse, in der eine Dosisexposition der Magen- bzw. Duodenalschleimhaut von mehr als 14 Gy/ml mit einen erheblichen Ulzerarisiko

vergesellschaftet ist. In einer Subanalyse dokumentierten Mohnike et al. bei 57 Patienten, bei denen der GI-Trakt nach einer iBT einer Mindestexposition von 1 Gy/cm³ ausgesetzt war, eine Ulzerationsrate von 4,2 % (3 Patienten). Durch den Einsatz einer Prophylaxe mit Protonenpumpenhemmer im Falle einer kritischen Exposition von Magen und Darm wird das Ulzerarisiko gesenkt (66). Insbesondere bei linkshepatischer Ablation steigt aufgrund der anatomischen Nähe zum oberen GI-Trakt das Risiko, Dosisgrenzwerte benachbarter Organe zu überschreiten. Eine folgerichtige Dosisreduktion (der tumorumschließenden Dosis) zur Sicherheit der benachbarten Organe erhöht jedoch das Risiko, Tumorrandrezidive auszubilden (56). Eine alternative Möglichkeit scheint die oben ausführlich beschriebene interventionelle Distanzierung des Risikoorgans mittels Ballonkatheter zu sein, die eine hohe tumorumschließende Dosis im Zielvolumen bei gleichzeitiger Schonung von Risikoorganen wie Magen und Darm ermöglicht (88) **(Publikation 7)**.

Obwohl in Studien eine sichere und effektive Anwendung der iBT an zentralen, hilusnahen Tumoren aufgezeigt werden konnte (58,89), muss berücksichtigt werden, dass das Risiko radiogen induzierter Gallengangsstenosen mit der Höhe der Gallengangsexposition steigt. Powerski et al. konnten hierfür einen Schwellenwert an den zentralen Gallengängen von 20,8 Gy ermitteln. Die postinterventionell bildmorphologisch (CT oder MRT) erfassten Cholestasen entwickelten sich nach 17 Monaten im Median (Range: 3–54 Monate). Die posthepatische Cholestase war mit einem erhöhten Abszessrisiko assoziiert (18 %), hatte jedoch im Vergleich zu Patienten ohne Cholestase keine Auswirkung auf das mediane Überleben (90). Dennoch muss insbesondere im Hinblick auf das Abszessrisiko erwähnt sein, dass es sich in der Studie von Powerski et al. allesamt um Patienten ohne vorherige Gallengangsmanipulation (z. B. ERCP) handelte. Gallengangsmanipulationen erhöhen nochmals das Risiko postinterventioneller Infektionen. In der klinischen Routine erfolgt bei erhöhtem Risiko einer Cholestase/Infektion eine prophylaktische, periinterventionelle antibiotische Abdeckung.

3 Sicherheitsanalysen der iBT jenseits des hepatozellulären und metastasierten kolorektalen Karzinoms

Bei allen in den folgenden Sicherheitsanalysen eingeschlossenen Patienten handelt es sich um Patienten mit metastasierter Tumorerkrankung, die bereits eine Reihe an Vortherapien (Systemtherapie, Resektion) erhalten haben. Die Indikation zur iBT wurde in einem interdisziplinären Tumorboard gestellt, wenn eine Resektion aus technischen oder medizinischen Gründen nicht möglich war oder vom Patienten abgelehnt wurde. Häufig wurde aufgrund des reduzierten Allgemeinzustands von Patienten und des damit verbundenen postoperativen Mortalitätsrisikos gegen eine Resektion entschieden. Zudem erhielten häufiger Patienten eine lokale Ablation, die Metastasen in mehr als einem Organ aufwiesen. Dieses Phänomen der negativen Patientenselektion wird vermehrt in Studien zu lokalen Ablationen beobachtet und sollte in der Beurteilung der Ergebnisse berücksichtigt werden. Limitationen der folgenden Studien sind das retrospektive Design, das kleine Patientenkollektiv sowie die Heterogenität der Patienten.

3.1 Nierenzellkarzinom

Mit nur etwa 2 % macht das Nierenzellkarzinom lediglich einen kleinen Anteil aller Tumorerkrankungen aus. Die Inzidenz des Nierenzellkarzinoms, insbesondere im Frühstadium, stieg in den letzten Jahren stetig an. Verantwortlich hierfür sind die zufällig entdeckten Nierenzellkarzinome im Rahmen bildgebender abdomineller Untersuchungen (91). Für das lokale Nierenzellkarzinom stellt die chirurgische Resektion den einzig kurativen Ansatz dar (92). In jedoch 17–20 % der Fälle lassen sich bereits bei Diagnosestellung Fernmetastasen diagnostizieren. 40–50 % der lokal fortgeschrittenen Nierenzellkarzinome entwickeln im weiteren Verlauf Metastasen. Während kleine Nierenzellkarzinome im Stadium I unbehandelt eine 5-Jahres-Überlebensrate von 97 % aufweisen, sinkt diese bei lokal fortgeschrittenem oder metastasiertem Stadium auf nur noch 14 % ab (92). Eine deutliche Verbesserung des Überlebens wurde durch die im Jahr 2005 eingeführten zielgerichteten Therapeutika erreicht. Aktuell stehen 7 Substanzen zur Verfügung (5 VEGF-Inhibitoren und 2 mTOR-Inhibitoren). Das mediane Gesamtüberleben konnte im Vergleich zur nicht spezifischen Immuntherapie mit Zytokinen von 13,3 Monaten auf ca. 29 Monate angehoben werden (92). Die zielgerichtete Therapie hat sich demnach zur Erstlinientherapie des fortgeschrittenen und/oder me-

tastasierten Nierenzellkarzinoms etabliert. Nachteilig ist das Risikoprofil der Substanzen, bspw. entwickeln etwa 17–40 % der Patienten einen Hypertonus sowie 10 % Blutbildveränderungen. Weitere mögliche Nebenwirkungen sind Nierenversagen, Lebertoxizität, kardiale Nebenwirkungen und Depressionen. Dies ist auch der Hauptgrund dafür, weshalb eine Kombinationstherapie der Substanzen nicht zugelassen ist (92). Hinsichtlich der lokalen Metastasentherapie liegen keine randomisierten Daten vor. In einer Metaanalyse (16 Studien, 2350 Patienten mit metastasiertem Nierenzellkarzinom) zur lokalen Metastasenbehandlung an unterschiedlichen Organen zeigten Dabestani et al. einen Überlebensvorteil für Patienten mit kompletter Metastasenentfernung. Für die Resektion von Lebermetastasen eines Nierenzellkarzinoms konnten Staehler et al. in einer retrospektiven Analyse an 88 Patienten einen wesentlichen 5-Jahres-Überlebensvorteil für die Resektionsgruppe herausarbeiten (62 % vs. 29 % ohne Metastasenresektion) (93). Dennoch sollte die in einer Metaanalyse von Pikoulis et al. dokumentierte postoperative Morbiditäts- und Mortalitätsrate von 18,2–57,1 % und 0–31 % nach Resektionen von Lebermetastasen bei Nierenzellkarzinomen berücksichtigt werden. Zudem treten Metastasen beim Nierenzellkarzinom lediglich in 5 % isoliert in der Leber auf (94). Weitere chirurgische Limitationen, wie ein zu geringes Leberrestvolumen oder ein reduzierter Allgemeinzustand des Patienten, erhöhen den Bedarf an alternativen lokalen Therapien, zumal in der S3-Leitlinie des Nierenzellkarzinoms keine generelle Empfehlung zur Metastasenresektion ausgesprochen wird (95).

In einer retrospektiven Analyse konnte die hohe Sicherheit und Effektivität der lokalen Radioablation von Lebermetastasen eines Nierenzellkarzinoms aufgezeigt werden. Eingeschlossen wurden 14 Patienten mit synchronen (3) und metachronen (11) Lebermetastasen **(Publikation 1)**. Bei allen Patienten war der Primarius bereits reseziert worden. 11 der 14 Patienten hatten bereits eine Erst- oder Zweitlinientherapie und waren darunter in der letzten Nachsorge progredient. 3 Patienten waren systemtherapienaiv, entweder aufgrund eines reduzierten Allgemeinzustands oder weil sie eine Systemtherapie ablehnten. Insgesamt wurde bei 54 mittels CT- oder MRT-gestützter Brachytherapie behandelten Lebermetastasen eine lokale Kontrollrate von 92,6 % bei einem medianen Beobachtungszeitraum von 10,2 Monaten (Range: 2,4–73,6 Monate) erreicht. Die mediane Metastasengröße war 2,9 cm (Range: 0,7–13,9 cm). Die tumorumschließende Dosis belief sich im Median auf 16,1 Gy. Keine Major-Komplikation wurde verzeichnet. Dieses Ergebnis der lokalen Kontrolle ist vergleichbar mit den in

der Literatur begrenzt vorhandenen Ergebnissen nach einer stereotaktischen Bestrahlungstherapie von Nierenzellkarzinommetastasen: So wurde in einer Studie von Stinauer et al. mit der SBRT von Nierenzellkarzinomen (20 % Lebermetastasen) bei einem medianen Gesamtüberleben von 22 Monaten eine lokale Kontrollrate von 88 % erreicht. Bemerkenswerterweise wurde in unserer Arbeit ein medianes Gesamtüberleben von 51,2 Monaten (Range: 10,2–81,5 Monate) mit drei Langzeitüberlebenden (51,5, 64,8 und 81,5 Monaten) verzeichnet, wenngleich erwähnt werden muss, dass 7 Patienten im Anschluss an die iBT mit einer Systemtherapie weiterbehandelt wurden.

Für selektionierte Patienten mit hepatisch metastasiertem Nierenzellkarzinom erscheint die iBT demnach ein vielversprechendes alternatives Verfahren zur lokalen Metastasentherapie zu sein.

3.2 Gastrointestinale Stromatumore

Gastrointestinale Stromatumore (GIST) sind die häufigsten mesenchymalen Tumore des Gastrointestinaltrakts und treten gehäuft im Magen (50–60 %) und im Dünndarm (20–30 %) auf (96). Metachrone Metastasen treten bei 23–47 % der Patienten auf, synchrone Metastasen bei 15–20 % (96). Die Therapie der Wahl im metastasierten Stadium ist eine Systemtherapie mit dem Tyrosinkinaseinhibitor Imatinib (97).

Um den Stellenwert einer lokalen Ablation von GIST-Metastasen besser einordnen zu können, bedarf es eines kurzen Einblicks in die Pathogenese der GIST. GIST entstehen aus den interstitiellen Zellen von Cajal, die als Schrittmacherzellen an der Kontrolle der Magen- und Darmmotilität beteiligt sind. Gain-of-Function-Mutationen im KIT-Gen (80–85 %) sowie im PDGFRA-Gen (7 %), die für einen Tyrosinkinaserezeptor codieren, stellen die häufigste genetische Ursache für die Entstehung von GIST dar (98). Ein wesentlicher Fortschritt in der Therapie der GIST wurde demnach mit der Einführung von Tyrosinkinase-Inhibitoren (TKI) erreicht – das mediane Gesamtüberleben im metastasierten Stadium konnte von weniger als 24 Monaten (ohne Tyrosinkinaseinhibitoren) auf 45–57 Monate (mit Tyrosinkinaseinhibitoren) angehoben werden (99,100). Mutationen im KIT Exon 11 sind mit einem längerem Gesamtüberleben vergesellschaftet als Mutation im KIT Exon 9 (66 vs. 38 Monate) (101).

Eine wesentliche Herausforderung in der Behandlung von GIST stellt die Imatinib-Resistenz dar. Eine primäre Imatinib-Resistenz, definiert durch eine Tumorprogression in den ersten 3–6 Therapiemonaten mit Imatinib, wird bei 10 % der GIST beobachtet (102). Etwa 50 % der initial auf Imatinib ansprechenden Tumore entwickeln typischerweise nach 18–24 Monaten eine sekundäre Imatinib-Resistenz auf der Grundlage einer sekundären Mutation. Die Wahrscheinlichkeit, eine Imatinib-Resistenz/klonale Selektion zu entwickeln, steigt mit der Anzahl an Tumorzellen, die einer Imatinib-Therapie ausgesetzt werden. Bei Imatinib-Versagen ist Sunitinib als Zweitlinientherapie zugelassen. Sunitinib-Mono als Zweitlinientherapie bei Imatinib-Versagen erreicht in Abhängigkeit vom KIT-Mutationsstatus ein medianes Gesamtüberleben zwischen 12 (KIT-Exon-11-Mutation) und 28 Monaten (KIT-Exon-9-Mutation) (103–105).

Bei Oligometastasierung empfehlen die ESMO (European Society for Medical Oncology) und die NCCN Guidelines (National Comprehensive Cancer Network) zusätzlich zur Systemtherapie einen komplementären Einsatz einer lokalen Therapie (Resektion, RFA oder [Chemo-]Embolisation). Ziel einer komplementären lokalen Therapie ist zum

einen die Reduktion einer klonalen Selektion/TKI-Resistenz. Zum anderen suggerieren Ford et al. in einer Studie, dass eine Zytoreduktion dem negativen Einfluss einer KIT-Exon-9-Mutation entgegenwirkt, die als wichtigster negativer Prognosefaktor gilt (106).

Über den Stellenwert der chirurgischen Resektion von GIST-Metastasen wird in der Literatur kontrovers diskutiert. Während Raut et al. ein verlängertes medianes Gesamtüberleben (29,8 Monate) nach Resektionen von Lebermetastasen annehmen (107), verweisen die NCCN Guidelines auf die hohe Komplikations- und R1-Rate nach Resektionen hin. Zudem muss das Risiko von Abtropfmetastasen mit nachfolgender Peritonealkarzinose berücksichtigt werden. Wird die komplementäre Metastasenchirurgie lediglich bei Patienten mit Sunitinib-Versagen durchgeführt, sinkt das mediane Gesamtüberleben auf 18,9 Monate (108).

Eine alternative komplementäre lokale Therapie stellt die Radiofrequenzablation dar. Daten zur RFA von GIST-Metastasen sind auf wenige retrospektive Studien begrenzt. In einer Analyse von Pawlik et al. wurden 66 Patienten mit hepatischen GIST-Metastasen einer Resektion und/oder einer intraoperativen RFA unterzogen. Das mediane Gesamtüberleben nach alleiniger RFA oder in Kombination mit einer Resektion lag bei 33,2 Monaten (109).

In unserer Arbeit zur Sicherheitsanalyse der iBT bei peritonealen und hepatischen GIST-Metastasen wurde bei 10 Patienten ein medianes Gesamtüberleben von 37,3 Monaten erreicht **(Publikation 3)**. Demnach erscheint auch in unserer Analyse eine zusätzliche lokale Metastasentherapie bei selektierten Imatinib-refraktären Patienten einen Überlebensvorteil gegenüber Sunitinib-Mono generieren zu können. Hervorzuheben an unserer Studie ist zum einen, dass zum Zeitpunkt der Datenerhebung noch 4 Patienten am Leben waren, sowie zum anderen das fortgeschrittene Stadium, in dem sich die Patienten zum Zeitpunkt der iBT befanden: Alle Patienten waren unter Imatinib, 5 Patienten bereits unter Sunitinib (Zweitlinientherapie) progredient. Dennoch ist das erreichte Gesamtüberleben von 37,3 Monaten höher als in den oben genannten Vergleichsstudien der Metastasenchirurgie und Radiofrequenzablation.

Bei insgesamt 30 vorgenommenen CT- oder MRT-geführten iBT von 40 Metastasen (30 hepatisch und 10 peritoneal) konnte bei einem medianen Beobachtungszeitraum von 25 Monaten eine exzellente lokale Kontrollrate von 97,5 % sowie ein progressionsfreies Überleben von 6,8 Monaten erreicht werden. 2 Major-Komplikationen (6,7 %)

wurden verzeichnet. Im Vergleich hierzu wurde in der Studie von Yeh et al. bei Patienten mit Sunitinib-Versagen und komplementärer Metastasenchirurgie eine Major-Komplikationsrate von 15 % verzeichnet (108). Demzufolge erscheint die iBT als ein sicheres und effektives Verfahren zur lokalen Behandlung von GIST-Metastasen.

3.3 Magenkarzinom

Wenn auch die Inzidenz des Magenkarzinoms in den westlichen Ländern seit Jahren rückläufig ist, bleibt es weltweit die zweithäufigste Krebstodesursache (110,111). Therapie der Wahl bei lokal begrenztem Magenkarzinom ist die Gastrektomie mit lokaler Lymphadenektomie in Abhängigkeit vom Tumorstadium verknüpft mit einer neoadjuvanten und/oder adjuvanten Chemotherapie (112). Magenkarzinome werden jedoch etwa in zwei Drittel der Fälle (außer in Japan) im fortgeschrittenen oder bereits metastasierten Stadium entdeckt (110). Bei Erstdiagnose haben bereits 4–14 % der Patienten Lebermetastasen (113). Außerdem entwickeln etwa 25–30 % nach initial kurativer Gastrektomie im weiteren Verlauf Fernmetastasen (114). Im metastasierten Stadium gilt unabhängig vom Ausmaß der Metastasierung die rein palliative systemische Chemotherapie als Standarttherapie (112). Ohne Therapie liegt das mediane Gesamtüberleben bei nur 3–5 Monaten. Das 2-Jahres-Überleben liegt bei unter 10 %. Auch mit einer palliativen Chemotherapie liegt das mediane Gesamtüberleben des metastasierten Magenkarzinoms bei lediglich etwa einem Jahr (115). Obwohl vereinzelt Studien einen Überlebensvorteil nach operativer Entfernung von Metastasen suggerieren, wird in der S3-Leitlinie eine Resektion von Primärtumor und Metastasen außerhalb von Studien nicht empfohlen, da bis dato prospektiv randomisierte Studien fehlen (112). Dennoch scheinen folgende Subgruppen an Patienten von einer Metastasenresektion zu profitieren:

1. Patienten bis 70 Jahre (116),
2. Patienten mit begrenztem Metastasierungsmuster (Leber- oder Lymphknotenmetastasen) (117) und
3. Patienten, die gut auf eine vorausgegangene Chemotherapie ansprechen (118).

Ein vielversprechendes Ergebnis liefert die prospektive, wenngleich nicht randomisierte AIO-FLOT3-Studie von Al-Batran et al. In dieser Arbeit konnte bei Patienten mit limitierter Metastasierung ein beachtlicher Überlebensvorteil durch eine zusätzlich zur Chemotherapie durchgeführte Metastasenresektion erzeugt werden (31,3 Monate vs.

15,9 Monate). Patienten mit retroperitonealen Metastasen profitierten stärker als Patienten mit hepatischen Metastasen (20). Verantwortlich für dieses gute Ergebnis ist vermutlich die sorgfältig durchgeführte Patientenselektion, zumal die asiatische prospektive Phase-III-Studie REGATTA bei weniger selektionierten Patienten keinen Überlebensvorteil durch eine Metastasenresektion beim metastasierten Magenkarzinom verzeichnen konnte (119). In einer aktuell in Deutschland laufenden RENAISSANCE/FLOT5-Studie wird der Überlebensvorteil einer nach Chemotherapie durchgeführten Resektion bei einer selektierten Subgruppe an Patienten mit metastasiertem Magenkarzinom prospektiv randomisiert untersucht.

Jedenfalls zeigt ein großer Teil der Magenkarzinom-Patienten ein Metastasierungsmuster mit gleichzeitigem Befall mehrerer Organe (peritoneal, lymphatisch, hepatisch, pulmonal). Für diese Patienten wird kein Überlebensvorteil durch eine Metastasenresektion angenommen (116). Alternative, minimalinvasive Verfahren zur lokalen Metastasentherapie des Magenkarzinoms wurden in nur wenigen retrospektiven Arbeiten untersucht (120,121).

In unserer Studie zur lokalen Metastasentherapie des Magenkarzinoms wurden 12 Patienten mit insgesamt 40 Metastasen (29 Leber-, 2 Pankreas- und 5 Lymphknotenmetastasen) nach multidisziplinärer Therapieentscheidung mittels CT- oder MRT-geführter Brachytherapie behandelt **(Publikation 5)**. Die mediane Metastasengröße war 2 cm (Range: 1–10,2 cm). Mit einer medianen tumorumschließenden Dosis von 19,9 Gy konnte eine lokale Kontrolle in 89 % erreicht werden. Insgesamt zeigten sich 4 Lokalrezidive (2 Lebermetastasen, 1 Pankreas- und 1 Lymphknotenmetastase) bei 3 Patienten. Das mediane progressionsfreie Überleben belief sich auf 6,5 Monate. Das erreichte mediane Gesamtüberleben von 11,4 Monaten nach iBT ist vergleichbar mit dem Gesamtüberleben des metastasierten Magenkarzinoms nach alleiniger Systemtherapie, gleichwohl unser Patientenkollektiv ausschließlich Patienten erfasst, die unter Systemtherapie bereits progredient waren (negative Selektion).

Demnach erscheint insbesondere in der Salvage-Situation des metastasierten Magenkarzinoms oder wenn eine Metastasenresektion aus irgendeinem Grund nicht möglich ist, die iBT als ein sicheres Verfahren zur lokalen Metastasentherapie mit anscheinend positivem Einfluss auf das Gesamtüberleben.

3.4 Ösophaguskarzinom

Ösophaguskarzinome werden in über 50 % der Fälle in einem bereits lokal fortgeschrittenen oder metastasierten Tumorstadium (Stadium IV) diagnostiziert (122,123). Eine Resektion in kurativer Intention ist in diesem Stadium nicht mehr möglich. Zudem entwickeln etwa 50 % der initial in kurativer Intention resezierten Patienten innerhalb von 3 Jahren ein Lokalrezidiv oder Fernmetastasen (122,123). Bei einem Rezidiv oder bei Auftreten von Fernmetastasen ist das Gesamtüberleben mit 3–7 Monaten deutlich eingeschränkt (122,123). Insgesamt gilt für das Ösophaguskarzinom ein 5-Jahres-Gesamtüberleben von 15–25 % (124,125).

Bis heute stehen im lokal fortgeschrittenen oder metastasierten Stadium nur palliative Therapieoptionen zur Verfügung. Vielmehr noch gibt es für das Plattenepithelkarzinom im Stadium IV keine Systemtherapie, die einen relevanten lebensverlängernden Effekt erbringt. Ein multimodales Therapiekonzept ist in der S3-Leitlinie für das Stadium IV nicht vorgesehen (126). Wenige retrospektive Studien weisen jedoch auf einen Überlebensvorteil nach aggressiver Metastasentherapie hin. So konnten Van Daele et al. nach einem multimodalem Vorgehen beim metastasierten Ösophaguskarzinom mit aggressiver Metastasentherapie (Resektion, RFA, MWA) plus Systemtherapie ein medianes Gesamtüberleben von 22 Monaten verzeichnen (127). Auch Mariette et al. und Badgwell et al. suggerieren für Patienten mit metastasiertem Ösophaguskarzinom einen Überlebensvorteil bei multimodaler Therapie mit Metastasenresektion (122,128) Jedoch zeigten viele Studien zur Metastasenresektion eine erhöhte Morbidität und Mortalität (126). Dies sollte bei der Therapieentscheidung berücksichtigt werden.

Deutlich weniger invasiv und mit geringen Komplikationsraten assoziiert ist die bildgeführte interstitielle Brachytherapie. Zur Evaluierung der Durchführbarkeit und Sicherheit der iBT bei Metastasen eines Ösophagus-Plattenepithelkarzinoms wurden in unserem Institut 11 Patienten mit 21 nicht resektablen Metastasen untersucht **(Publikation 4)**. Alle Patienten (8 metachron, 3 synchron metastasiert) wiesen unter palliativer Chemotherapie einen Tumorprogress auf. Die Metastasen (14 viszeral, 7 pulmonal) hatten einen medianen Durchmesser von 2,2 cm (Range: 0,9–6,8 cm) und wurden im Median mit 20,1 Gy tumorumschließend behandelt. In einem Beobachtungszeitraum von 6,3 Monaten konnte eine lokale Kontrolle von 85,7 % erreicht werden. Vergleichbare lokale Kontrollraten (74,2 und 83,0 %) verzeichnet die Radiofrequenzablation bei der Behandlung von Lungenmetastasen eines Ösophaguskarzinoms (129,130). Das

progressionsfreie Überleben in unserer Studie war mit lediglich 3,4 Monaten sehr kurz. Zu einem sehr ähnlichen Ergebnis mit einem progressionsfreien Überleben von 3,5 Monaten gelangen Geisel et al. in ihrer Sicherheitsanalyse der iBT zur Behandlung von Metastasen eines Ösophagus-Adenokarzinoms (121). Das auffällig kurze progressionsfreie Überleben deutet auf die biologische Aggressivität der Tumore hin. Im Vergleich zum in der Literatur beschriebenen Gesamtüberleben von 6–10 Monaten für das Stadium IV konnte in unserer Studie trotz des höchstpalliativen Patientenkollektivs mit bereits unter palliativer Chemotherapie progredienten Tumoren noch ein medianes Gesamtüberleben von 13,7 Monaten (Range: 5,6–25,7 Monate) erreicht werden. Hervorzuheben ist zudem das in der Literatur beschriebene geringe Komplikationsrisiko der iBT mit 3–4 % Major-Komplikationen (66). In unserer Studie wurde bei insgesamt 19 durchgeführten CT- oder MRT-gestützten interstitiellen Brachytherapien keine Major-Komplikation beobachtet.

Somit konnte auch in dieser Studie die Sicherheit und Effektivität der iBT aufgezeigt werden. Dennoch sollte im Hinblick auf die aggressive Natur des Ösophaguskarzinoms eine sorgfältige Patientenselektion durchgeführt werden.

3.5 Analkarzinom

In den letzten Dekaden ist die Inzidenz des Analkarzinoms stetig gestiegen (131,132). Der häufigste Auslöser ist der humane Papillomavirus (HPV). Eine chirurgische Resektion in kurativer Intention in nach europäischer und US-amerikanischer Leitlinie nur bei gut differenzierten T1-, N0-Analrandkarzinomen vorgesehen. Basierend auf den sogenannten Nigro-Studien gilt seit 1974 für das lokal begrenzte Plattenepithelkarzinom des Analkanals die kombinierte Radiochemotherapie als Goldstandard (133–135). Damit konnte ein 5-Jahres-Überleben von 44–78 % erreicht werden (136). Nach einem Lokalrezidiv ist die Prognose mit einem Gesamtüberleben von 8–15 Monaten sehr schlecht (131,137–139). Bei einem Lokalrezidiv, einem Resttumor nach Radiochemotherapie oder weit fortgeschrittenem Tumor mit Infiltration von Nachbarorganen, stellt die Rektumexstirpation die einzige Salvage-Therapie dar. Etwa 10–20 % der Patienten mit Analkarzinom haben bereits bei Erstdiagnose oder entwickeln im weiteren Verlauf Fernmetastasen, für die es keine Standarttherapie gibt (140). Zum Einsatz kommen häufig 5-Fluorouracil und Cisplatin als palliative Chemotherapie. Mit dieser Kombinationstherapie erreichen Patienten mit metastasiertem Analkarzinom in der Studie von Faivre et al. ein medianes Gesamtüberleben von 34,5 Monaten (141). In einer an 10 Zentren in den USA durchgeführten einarmigen, multizentrischen Phase-II-Studie wurden 37 Patienten mit therapierefraktärem metastasierten Analkarzinom mit dem monoklonalen Antikörper Nivolumab behandelt. Hierunter zeigten 24 % ein objektives Ansprechen. Insgesamt wurde ein medianes Gesamtüberleben von 11,5 Monaten erreicht (142). Des Weiteren verweist die NCCN auf die Möglichkeit einer Resektion von Fernmetastasen nach Diskussion im interdisziplinären Tumorboard, obgleich die Datenlage hinsichtlich der Effektivität einer Metastasentherapie beim metastasierten Analkarzinom limitiert ist. In den Studien von Omich et al. und Pawlik et al. wurden bei 28 bzw. 55 Patienten Lebermetastasen von Plattenepithelkarzinomen reseziert, darunter 19 bzw. 27 Analkarzinome. Die Studien zeigten ein medianes Gesamtüberleben von 33,3 bzw. 22,3 Monaten für alle Plattenepithelkarzinome und ein progressionsfreies Überleben von 9,3 bzw. 9,8 Monaten (143,144). Weitere Studien suggerieren beim metastasierten Analkarzinom einen Überlebensvorteil nach multimodaler Therapie. So zeigen Eng et al. für eine Patientengruppe, die einem multimodalen Therapiekonzept (Systemtherapie + Metastasentherapie mittels Resektion, RFA oder Radiatio) unterzogen wurde, einen deutlichen Überlebensvorteil gegenüber Patienten mit alleiniger Systemtherapie (53 vs. 22 Monate) sowie ein längeres progressionsfreies

Überleben (16 vs. 7 Monate) (145). Auch die Studie von Evesque et al. verzeichnet nach multimodaler Therapie (Systemtherapie + Metastasentherapie mittels Resektion, RFA oder Radiatio) des metastasierten Analkarzinoms einen Überlebensvorteil mit einem medianen Gesamtüberleben von 22 Monaten (146). Dies liegt deutlich unter dem in der Studie von Eng et al. erreichtem Gesamtüberleben. Grund hierfür ist am ehesten die Therapienaivität der Patienten in der Studie von Eng et al. ab dem Zeitpunkt der Metastasierung.

Bekannterweise sind der Metastasenchirurgie in der Leber Limitationen gesetzt: Komorbiditäten, Anzahl und Lokalisation der Metastasen sowie ein nicht ausreichend vorhandenes Lebervolumen machen ein operatives Vorgehen in etwa 70–80 % unmöglich (4). Auch die Radiofrequenzablation ist in ihrer technischen Anwendung begrenzt (46).

In einer unserer Analysen wurde deswegen die lokale Metastasentherapie mittels iBT bei 7 chemotherapeutisch vorbehandelten Patienten mit metastasiertem Analkarzinom evaluiert **(Publikation 10)**. Bei 4 Patienten traten die Metastasen synchron auf, bei 3 Patienten metachron. Bei insgesamt 38 nicht resektablen Metastasen (29 Leber-, 9 Lungenmetastasen und 1 Lymphknotenmetastase) wurde mittels CT- oder MRT-gestützter iBT eine exzellente lokale Kontrollrate von 97,4 % bei einem medianen Beobachtungszeitraum von 15,2 Monaten erreicht. Das progressionsfreie Überleben belief sich auf 3,3 Monate (Range: 2,5–32,6 Monate). Das mediane Gesamtüberleben belief sich auf 25,2 Monate und war damit vergleichbar mit den Ergebnissen der oben genannten Studie von Evesque et al. Bei 14 durchgeführten CT- oder MRT-gestützten interstitiellen Brachytherapien wurde keine Major-Komplikation verzeichnet. Demnach erscheint die bildgeführte iBT ein effektives minimalinvasives Werkzeug zu sein, das im Rahmen eines multimodalen Therapieansatzes beim metastasierten Analkarzinom eingesetzt werden kann. Über den Einsatz der iBT beim metastasierten Analkarzinom sollte jedoch im Einzelfall in einem multidisziplinären Tumorboard entschieden werden.

3.6 Pankreaskarzinom

Das Pankreaskarzinom ist die vierthäufigste Todesursache weltweit (125). Die Prognose ist mit einem 5-Jahres-Überleben von 2–5 % sehr schlecht (147,148). Grund hierfür ist das häufig zu spät entdeckte Pankreaskarzinom mit bereits fortgeschrittenem bzw. metastasiertem Stadium. Eine kurative Resektion ist bei lediglich 10–15 % möglich (149,150). Aufgrund häufiger Lokalrezidive und/oder der Entwicklung von Fernmetastasen im weiteren Krankheitsverlauf liegt das 5-Jahres-Gesamtüberleben trotz kurativer Resektion bei unter 20 % (151). Diesbezüglich ergaben einige präklinische Studien Hinweise auf eine bereits initial vorhandene mikrometastatische Ausbreitung des Pankreaskarzinoms (152). Das mediane Gesamtüberleben für Patienten mit Fernmetastasen liegt mit Gemcitabine als Erstlinientherapie bei etwa 6 Monaten, das 1-Jahres-Überleben bei 18–20 % (153,154). Eine Phase-III-Studie konnte für die Kombination aus Gemcitabine und Erlotinib eine geringe, dennoch signifikante Verbesserung des medianen Überlebens gegenüber Gemcitabine-Mono aufzeigen (155). Für eine Subgruppe von Patienten mit günstigem Risikoprofil konnte in einer randomisierten Studie ein wesentlicher Überlebensvorteil des FOLFIRINOX-Regimes (Kombination von 5-Fluorouracil/Folinsäure, Irinotecan Oxaliplatin) gegenüber Gemcitabine-Mono nachgewiesen werden (11,1 vs. 6,8 Monate) (156). Aufgrund der frühzeitigen Metastasierung mit häufig letaler Folge erscheint eine multimodale Herangehensweise zur Kontrolle der Metastasen sinnvoll, findet jedoch aufgrund ungünstiger/unzureichender Datenlage keinen Konsens in den Leitlinien. Während die Resektion bei anderen Entitäten (bspw. kolorektales Karzinom) den Goldstandard in der Metastasentherapie setzt, ist ihr Einsatz beim metastasierten Pankreaskarzinom umstritten. Einige Studien mit kleinem Patientenkollektiv zeigen einen geringen Überlebensvorteil nach Metastasenresektion eines Pankreaskarzinoms (157–159). In anderen Studien konnte kein signifikanter Überlebensvorteil erreicht werden (160,161): So zeigen Klempnauer et al. für Patienten mit synchroner bzw. metachroner Metastasenresektion ein medianes Gesamtüberleben von 5,8 Monaten bzw. 8,3 Monaten. Die perioperative Mortalität lag bei 4,3 % (158). In der Studie von Klein et al. wurde bei 22 Patienten mit synchroner Metastasenresektion ein medianes Gesamtüberleben von 7,6 Monaten erreicht. Es gibt nur vereinzelt veröffentliche Daten zum Einsatz minimalinvasiver Verfahren bei der Metastasentherapie des Pankreaskarzinoms. Hierzu berichten Park et al. in einer Studie an 34 Patienten über einen positiven Effekt auf das Gesamtüberleben nach RFA von Metastasen < 2 cm (162).

In unserer Studie wurden 45 Lebermetastasen von 16 chemotherapeutisch vorbehandelten Patienten minimalinvasiv mittels interstitieller Brachytherapie bestrahlt **(Publikation 11)**. 5 Patienten waren synchron, 11 Patienten metachron metastasiert. Die iBT wurde bei chemotherapeutisch austherapierten Patienten in einer sogenannten Salvage-Situation angewandt, um metastasenverursachte Komplikationen zu vermeiden. Die mediane Metastasengröße war 2,2 cm (Range: 1–11,2 cm). Mit einer medianen tumorumschließenden Dosis von 21 Gy (Zieldosis 20 Gy) konnte eine lokale Kontrolle in 87 % erreicht werden. Das mediane progressionsfreie Überleben lag bei 3,4 Monaten und das mediane Gesamtüberleben bei 8,9 Monaten (Range: 3,1–29,3 Monate). In Anbetracht der Tatsache, dass sich unsere Patienten in der sogenannten Salvage-Situation befanden, zeichnet sich in unserer Studie auch ein Überlebensvorteil nach iBT ab. Zu einem ähnlichen Ergebnis kommen Wieners et al. in ihrer Sicherheitsanalyse der iBT: Bei der Behandlung von 45 Pankreaskarzinommetastasen zeigten sich eine lokale Kontrollrate von 91 %, ein progressionsfreies Überleben von 3,2 Monaten und ein Gesamtüberleben von 8,6 Monaten (163). In unserer Studie entwickelten 3 Patienten, jeweils mit biliodigestiver Anastomose nach Pankreasresektion, postinterventionell einen Leberabszess. Das Vorhandensein einer biliodigestiven Anastomose stellt aufgrund der möglichen Keimbesiedlung der intrahepatischen Gallengänge ein erhöhtes Risiko zur Ausbildung intrahepatischer Abszesse dar. Alle 3 Abszesse konnten mittels Drainage und Antibiotika erfolgreich behandelt werden.

Damit konnte der sichere und effektive Einsatz der iBT in der Salvage-Situation des hepatisch metastasierten Pankreaskarzinoms verdeutlicht werden.

4 Zusammenfassung

Motiviert durch die Behandlungserfolge des multimodalen Therapiekonzepts (Systemtherapie + lokale Metastasentherapie) beim hepatisch metastasierten kolorektalen Karzinom (CLOCC-Studie) steigt auch die Attraktivität der lokalen Metastasentherapie bei anderen Tumorentitäten. Bis auf wenige Ausnahmen bleibt die chirurgische Resektion der Goldstandard der lokalen Metastasentherapie. Die Anwendung chirurgischer Resektionen ist jedoch aufgrund medizinischer und onkologischer Restriktionen nur begrenzt durchführbar. Demzufolge rücken lokale Ablationsverfahren in selektionierten Patienten immer stärker in den Vordergrund. Hierzu zählen bildgeführte interventionelle Verfahren, die von der Europäischen Gesellschaft für medizinische Onkologie (ESMO, European Society of Medical Oncology) insbesondere in der oligometastasierten Situation als etablierte lokale Therapieverfahren anerkannt wurden.

Das oligometastasierte Stadium gilt als eine Art intermediäres Stadium zwischen lokal begrenztem und systemisch gestreutem Tumor. Angenommen wird, dass eine lokale Metastasentherapie bei Patienten mit Oligometastasierung aufgrund der günstigeren Tumorbiologie zu einen verlängerten progressionsfreien Überleben und Gesamtüberleben führt. Bei Tumoren mit Absiedelung lediglich einzelner Metastasen kann die vollständige Entfernung aller Metastasen sogar eine Heilungschance hervorrufen.

Neben dem Prinzip der Oligometastasierung gilt das Konzept der „Deepness of Response“ als weitere onkologische Rationale der lokalen Tumorablation. Hierbei wird angenommen, dass eine bestimmte Tumorlast letal für den Patienten sei. Die Senkung der Tumorlast durch zytoreduktive Maßnahmen gewährt dem Patienten eine längere Zeit (Überlebenszeit) bis zum Erreichen der letalen Tumorlast.

Ein weiteres Ziel lokal ablativer Verfahren ist die Zerstörung klonaler Tumorselektionen, die vermutlich gemeinsam mit der Tumorheterogenität für das sogenannte Mixed Response nach einer Systemtherapie verantwortlich sind. Das Auftreten eines Mixed Response wird durch die heute intensiviert eingesetzte zielgerichtete Systemtherapie vermehrt beobachtet. Der konsolidierende Einsatz lokaler Ablationsverfahren beim Mixed Response destruiert genau diese klonalen, chemotherapieresistenten Zellen, sodass eine Umstellung der Systemtherapie herausgezögert bzw. dem Patienten eine vorübergehende systemtherapiefreie Zeit ermöglicht werden kann.

Die Radiofrequenzablation hat sich zur am häufigsten eingesetzten Ablationsmethode entwickelt. Als thermales Ablationsverfahren unterliegt die RFA in ihrer Anwendung jedoch einigen Limitationen: Tumorgröße > 5 cm, Vorhandensein angrenzender thermosensibler Risikostrukturen wie Gallengänge sowie Kühlungseffekte durch erhöhte Tumorvaskularisation oder umliegende Gefäße. Diese Limitationen haben einen unmittelbaren negativen Einfluss auf die lokale Kontrolle.

Ein in unserem Institut häufiger als die RFA Einsatz findendes lokales Ablationsverfahren ist die bildgeführte interstitielle Brachytherapie. Die iBT ist ein interdisziplinäres Verfahren zwischen der interventionellen Radiologie und der Strahlentherapie und zählt zu den hypofraktionierten strahlentherapeutischen Therapien. Ein wesentlicher Vorteil der iBT gegenüber der RFA ist die mögliche Anpassung der Bestrahlungsgeometrie (Isodosis-Linien) an die Tumorgeometrie. Zudem gilt für die iBT, anders als für die RFA, keine Limitation durch Tumorgröße, Kühlungseffekte oder angrenzenden hitzevulnerablen Strukturen wie Gallengänge.

Im Gegensatz zur SBRT, welche als dosishomogenes Verfahren mit Einzeldosen von etwa 10–20 Gy gilt, ermöglicht die intratumorale Platzierung einer Iridium^{192}-Strahlenquelle bei der iBT die Bestrahlung des Tumors von innen nach außen mit exorbitant hohen Dosen (< 50 Gy) im Tumorzentrum. Der konsekutive hohe zytotoxische Effekt ermöglicht eine effektive Bestrahlung auch von Tumoren, die für die konventionelle Bestrahlungsmethode (Normofraktionierung) als strahlungsresistent galten (Nierenzellkarzinome oder gastrointestinale Stromatumore).

Zudem führt der hohe zytotoxische Effekt der interstitiellen Brachytherapie zu einer hohen Nekroserate des behandelten Tumors. Im Vergleich zur transarteriellen Chemoembolisation (TACE) konnte für die iBT sowohl eine höhere Nekroserate, als auch eine verlängerte progressionsfreie Zeit bei hepatozellulären Karzinomen erreicht werden. Dies lässt die iBT als mögliche Alternative zur transarteriellen Chemoembolisation (TACE) im Bridging hepatozellulärer Karzinome vor Lebertransplantation erscheinen.

Aufgrund des raschen Abfalls der Strahlendosis mit zunehmendem Abstand zur Strahlenquelle können angrenzende strahlensensible Strukturen sowie das gesunde Parenchym des Zielorgans bestmöglich geschont werden. Exposition umliegender Risikoorgane jenseits der kritischen Grenzwerte stellen eine Limitation der iBT dar, können

jedoch mittels perkutan eingeführter Ballonkatheter vermieden werden. Die Ballonkatheter werden zwischen Risikoorgan und Zielläsion positioniert und können die Punktdosis (D1cc in Gy/cm³) am Risikoorgan signifikant reduzieren.

Als bildführende Modalität der iBT gilt die Computertomographie als Goldstandard. Die Positionierung der die Strahlenquelle tragenden Katheter erfolgt dabei unter CT-Fluoroskopie, welche eine Strahlenexposition für Patient und medizinischem Personal impliziert. In unserer Analyse konnte gezeigt werden, dass die Positionierung der Katheter auch Ultraschall-gestützt möglich ist und dadurch die CT-Fluoroskopiezeit pro Eingriff signifikant reduziert werden konnte. Eine weitere vorteilhafte bildführende Modalität stellen offene MRT-Sytseme dar, spielen jedoch auf Grund der begrenzten Verfügbarkeit eher eine untergeordnete Rolle.

Nach aktueller Studienlage konnte sich die perkutane, bildgeführte Brachytherapie als ein effektives und sicheres Verfahren in der Behandlung kolorektaler Lebermetastasen und des hepatozellulären Karzinoms etablieren und wurde von der ESMO (European Society of Medical Oncology) in die jeweilige Leitlinie aufgenommen.

In unseren Sicherheitsanalysen konnte die Effektivität und Sicherheit der bildgeführten interstitiellen Brachytherapie auch auf andere Lokalisationen (bspw. am Pankreas) und Entitäten ausgeweitet werden. Hepatische und extrahepatische Metastasen des Magenkarzinoms, Nierenzellkarzinoms, Analkarzinoms, Ösophaguskarzinoms, Pankreaskarzinoms und gastrointestinaler Stromatumore wurden mit hoher lokaler Kontrolle abladiert.

Nicht nur die sehr geringe Komplikationsrate (einschließlich der Ausbildung von Stichkanalmetastasen), sondern auch der in den Analysen suggerierte Überlebensvorteil nach einer iBT zeigt die Notwendigkeit für prospektive randomisierte Studien, um unsere aussichtsreichen Ergebnisse zur iBT zu validieren.

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Eidesstattliche Erklärung

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

Bildgeführte interstitielle Brachytherapie im Einsatz der multimodalen Therapie bei metastasierter Tumorerkrankung

in der Klinik für Radiologie und Nuklearmedizin unter Leitung von Prof. Dr. med. M. Pech ohne sonstige Hilfe durchgeführt 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/Universität zur Habilitation eingereicht.

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

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Originale der Publikationen

Publikation 1

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.

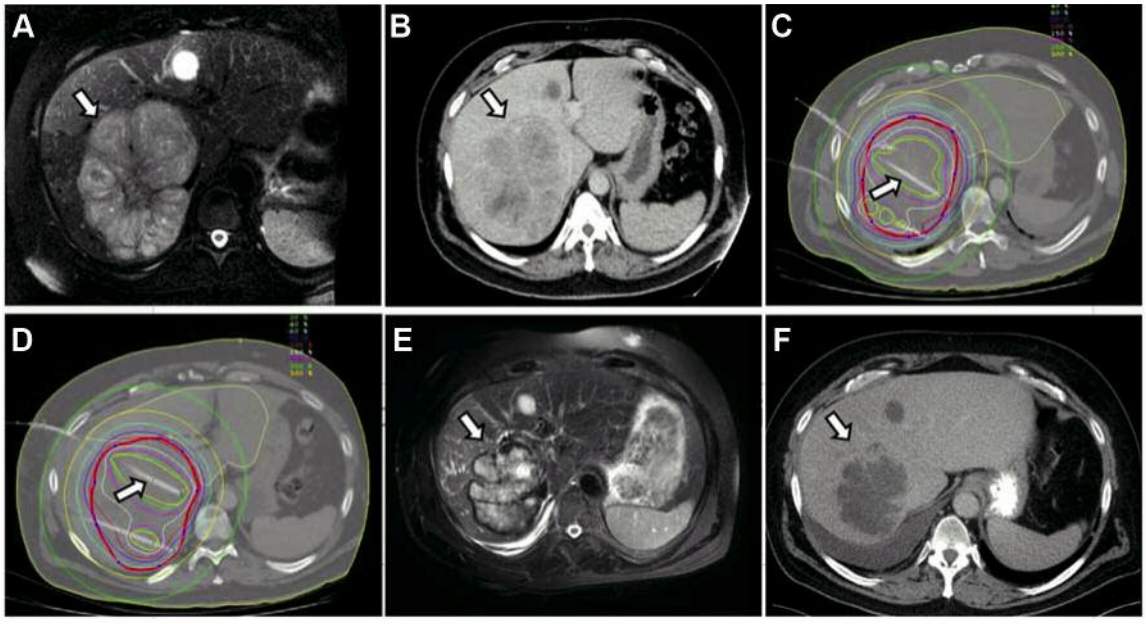

Figure 1. *Local tumor control in a patient with metastatic renal cell carcinoma in the right liver lobe. A/B: T2w MRI and pre-interventional contrast-enhanced CT: white arrow shows a metastasis from renal cell carcinoma in the left liver lobe prior to treatment by interstitial brachytherapy. C/D: Planning 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

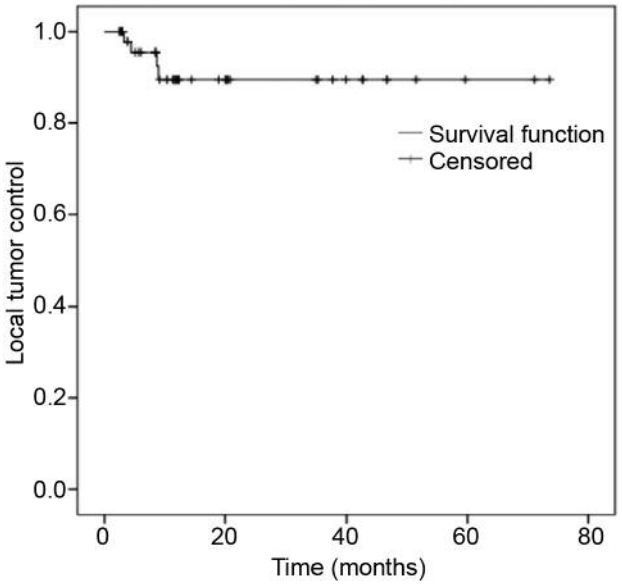

Figure 2. *Local tumor control after iBT of all treated mRCC.*

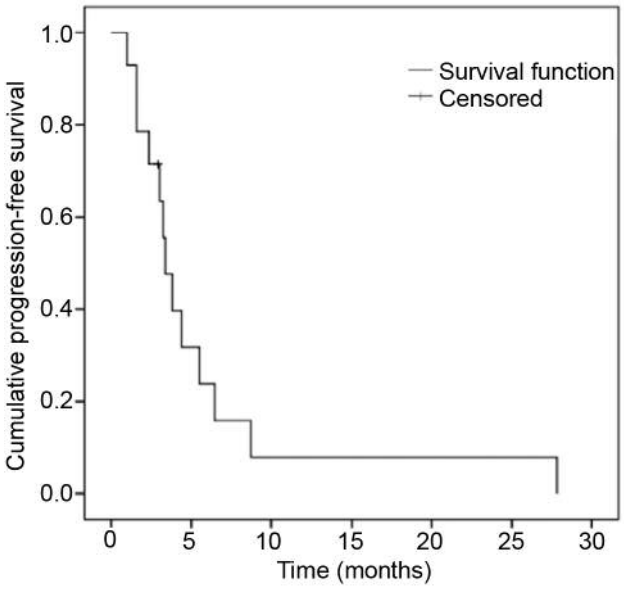

Figure 3. *Progression-free survival of patients with mRCC after iBT.*

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

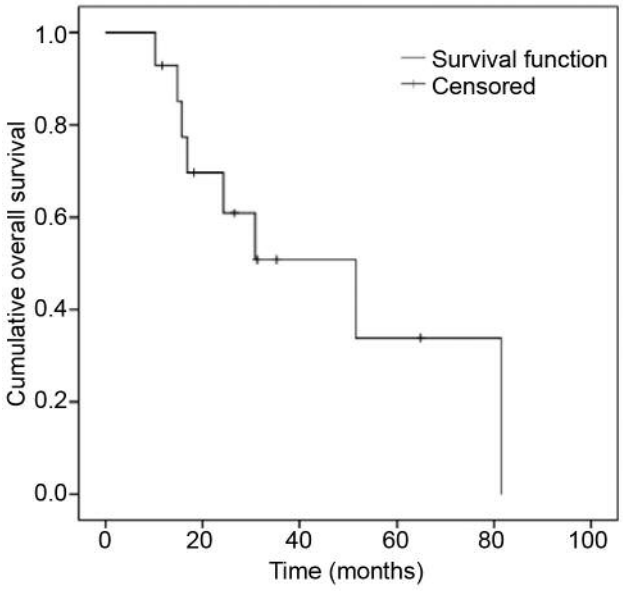

Figure 4. *Graph shows overall survival of all patients with mRCC ablated by interstitial brachytherapy.*

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.

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Research article

Efficacy and safety of CT-guided high-dose-rate interstitial brachytherapy in primary and secondary malignancies of the pancreas

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ABSTRACT

Purpose: To evaluate efficacy and safety of CT-guided iBT in patients with primary and secondary malignancies of the pancreas.

Material and methods: 13 patients with 13 lesions of the pancreatic corpus and tail were included: 8 secondary malignancies (metastatic lesions = ML) and 5 primary malignancies, including 3 primary tumors (PT) and 2 isolated locoregional recurrences (ILR) after surgical resection were treated with image-guided iBT using a 192iridium source (single fraction irradiation). Every 3 months after treatment clinical and imaging follow-up were conducted to evaluate efficacy. Peri- and postinterventional complications were assessed descriptively.

Results: The median diameter of the gross tumor volume (GTV) was 3 cm (range 1–6.5 cm), treated with a median D100 (minimal enclosing tumor dose) of 15.3 Gy (range 9.2–25.4 Gy). Local tumor control (LTC) was 92.3% within a median follow-up period of 6.7 months (range 3.2–55.7 months). Cumulative median progression free survival (PFS) was 6.2 months (range 2.8–25.7 months; PFS of primary and secondary malignancies was 5.8 and 6.2 months, respectively). Cumulative median over all survival (OS) after iBT was 16.2 months (range 3.3–55.7 months; OS of primary and secondary malignancies was 7.4 months and 45.6 months, respectively). 1 patient developed mild acute pancreatits post iBT, spontanously resolved within 1 week. No severe adverse events (grade 3+) were recorded.

Conclusion: Image-guided iBT is a safe and particularly effective treatment in patients with primary and secondary malignancies of the pancreas and might provide a well-tolerated additional therapeutic option in the multidisciplinary management of selected patients.

1. Introduction

Treatment of advanced or metastatic disease is challenging and best approached by a multidisciplinary team with an increasing tendency towards an individually tailored anticancer therapy to achieve the best possible outcomes. In this context the significance of local ablative techniques is constantly rising. Out of the toolbox of local ablation techniques high-dose-rate interstitial Brachytherapy (HDR-iBT = iBT) is a well-tolerated catheter-based afterloading method and it has been shown to provide high tumor control rates in primary and secondary malignancies of the liver, such as hepatocellular carcinoma and particularly in metastatic colorectal carcinoma, demonstrating local tumor control (LTC) rates of 95% and 88.3% after 12 months, respectively [1–3].

Furthermore, favorable LTC rates have also been achieved in the ablation of primary and secondary lung malignancies with a LTC rate of 91% at 12 months [4,5].

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease with a varying 5-year survival rate of 0.5–9% [6]. Complete resections remains the only potential cure, however, more than 80% of the

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patients are diagnosed with locally advanced or metastatic PDAC and therefore are not suitable for resection [7]. Furthermore, despite advances in surgical techniques and postoperative management pancreatic resection is still associated with substantial morbidity and mortality [8,9]. Additionally, about one third of the patients undergoing pancreaticoduodenectomy develop isolated locoregional recurrence (ILR) [10]. However, despite many therapeutic developments only moderate achievements regarding outcome and survival have been made over the last decades and especially in patients with locally advanced/unresectable or recurrent disease treatment options are scarce [11–13].

Apart from numerous studies considering therapy of PDAC little data exists regarding secondary malignancies of the pancreas; the estimated incidence of clinical occurrence of isolated metastatic lesions (ML) to the pancreas is about 2–5 % of all pancreatic neoplasm and in the majority of cases the represented primary tumor are renal, lung, colorectal or breast cancer and sarcoma [14,15]. Therapeutic options including resection depend on the type of primary tumor, location and number/volume of metastatic lesions and the patient's performance status.

In contrast, local ablative techniques, such as iBT provide a safe and minimal invasive approach and might offer an additional therapeutic option in the management of pancreatic neoplasms. To our knowledge no data has been published so far evaluating safety and efficacy of iBT in the ablation of primary and secondary malignancies of the pancreas. In this study we retrospectively analyzed a cohort of 13 patients with 13 inoperable lesions of the pancreas who underwent image-guided iBT.

2. Material and methods

2.1. Eligibility criteria and patients characteristics

Patient recruitment took place in a German university clinic, between October 2009 and February 2018. Indication for iBT was determined in an interdisciplinary tumor conference.

Principal inclusion criteria were: (a) unresectable neoplastic lesion of the pancreatic corpus or tail (including primary tumor = PT, ILR and ML), assessed by a surgeon with expertise in pancreatic malignancies, who considered them unresectable either due to tumor extent or medical comorbidities, (b) refusal of surgery, (c) East Coast Oncology Group (ECOG) performance status below 2. An upper limit was neither placed upon the number of lesions nor on the maximum tumor diameter. 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, Quick > 50%, partial thromboplastin time > 5 s) (d) lack of consent. The study was approved by the ethics committee of XXXXX (BLINDED).

In consideration of these criteria we included 13 patients (5 female and 8 male; median age 70 range 44–81) with one inoperable pancreatic lesion per patient (10 lesions of the pancreatic body and 3 lesions of the pancreatic tail). In detail: 3 PT (1 PDAC, 2 neuroendocrine tumors = NET), 2 ILR (PDAC) and 8 ML were treated, the latter comprised of 1 metastasis of gastric cancer, 1 breast cancer lesion and 6 renal cancer metastases. Out of these 8 patients with secondary malignancies 7 were presented with metachrone metastases. 11/13 patients had resection of the primary tumor, including 2 pylorus-preserving pancreaticoduodenectomy, followed by ILRs. 9/13 patients received palliative chemotherapy before iBT, including immune-checkpoint-inhibitors. Furthermore, 8/13 patients had additionally local ablative treatments of extrapancreatic metastases or the primary tumor prior to iBT; in detail: 1 iBT of lymphnode metastasis, 2 iBT of adrenal gland lesions, ablation of renal lesions (1 radiofrequency ablation, 3 iBTs) and 1 radioembolisation of the liver (for detailed patient characteristics see Table 1).

Prior to iBT all patients received a full clinical status evaluation with

Table 1
Patient characteristics.

Patient	Gender	Age	Location and Type of pancreatic neoplasm	Primary Tumor	Pathologic Subtypes	Maximum Diameter of the GTV (cm)	Administered D100 (Gy)	Local Recurrence (months after iBT)
1	m	75	ML of the corpus	gastric cancer	squamous cell carcinoma	4.3	12.0	6.7
2	m	77	ILR of the Corpus	pancreatic cancer	ductal adenocarcinoma	3	15.3	–
3	m	76	ILR of the Corpus	pancreatic cancer	ductal adenocarcinoma	3	9.2	–
4	m	69	PT of the cauda	pancreatic cancer	ductal adenocarcinoma	3	25.4	–
5	m	81	PT of the corpus	pancreatic cancer	neuroendocrine tumor	6.5	11.3	–
6	f	52	ML of the corpus	breast cancer	neuroendocrine tumor	4.5	17.4	–
7	f	44	PT of the corpus	pancreatic cancer	neuroendocrine tumor	2.5	10.3	–
8	f	73	ML of the corpus	renal cancer	clear cell renal cell carcinoma	1.3	15.8	–
9	m	73	ML of the caput	renal cancer	clear cell renal cell carcinoma	2.3	16.0	–
10	m	64	ML of the cauda	renal cancer	clear cell renal cell carcinoma	6.5	15.7	–
11	m	54	ML of the cauda	renal cancer	clear cell renal cell carcinoma	2.5	14.8	–
12	f	54	ML of the corpus	renal cancer	clear cell renal cell carcinoma	2.3	15.2	–
13	f	70	ML of the corpus	renal cancer	clear cell renal cell carcinoma	1	15.4	–

ML metastatic lesion, ILR isolated locoregional recurrence PT primary tumor.

a physical examination, laboratory assessment, whole body contrast-enhanced CT and Gb-EOB-DTPA-enhanced MRI (Primovist ®, Bayer, Pharma, Leverkusen, Germany) of the liver. Every 3 months after iBT clinical, laboratory and image-based follow-up (contrast-enhanced whole body CT) were performed.

2.2. Interventional procedure

The applied technique has been described elsewhere in detail [1,16,17]. Under guidance of a fluoroscopy-CT (Toshiba, Aquilion, Japan) an 18-gauge trocar puncture needle was inserted into the target lesions and a stiff angiography guide wire was exchanged for a flexible 6-F catheter sheath (Radifocus, Terumo™, Tokyo, Japan) using Seldinger's-technique followed by the placement of a 6-F afterloading catheter (Afterloadingkatheter, Primed® Medizintechnik GmbH, Halberstadt, Germany). The described intervention was performed under analgosedation (midazolam and fentanyl) and local anesthesia (lidocaine). The number and arrangement of the catheters was determined by the size, shape and anatomic location of the target. After catheter positioning a contrast-enhanced CT scan in breath-holding technique was acquired to document catheter positioning and for the purpose of irradiation planning. On these images the target lesion was carefully outlined as gross tumor volume (GTV), additionally, clinical target volume (CTV) and organs at risk (= OAR; e.g. stomach, duodenum) were marked by the interventional radiologist and the radiooncologist. Dose calculation was performed using the acquired dataset and 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 15 Gy was prescribed in our patients, which was defined as the minimum dose enclosing the complete CTV (D100). Inside the tumor higher doses were permitted and not limited. Additionally, dose limitations were taken into account due to adjacent OAR, 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 (Fig. 1 A–C illustrates the interventional method) [18].

2.3. Study design and statistical analysis

We retrospectively collected the data from our internally database ASENA® (LoeScap Technology GmbH). Primary endpoints were local tumor control (LTC) and safety; secondary endpoints were over all survival (OS) and progression free survival (PFS). The results were analyzed in a non-randomized and retrospective approach. Response Evaluation Criteria In Solid Tumors (RECIST vs1.1) were used to assess LTC and PFS. OS was calculated from the day of ablation to death. LTC, OS and PFS were evaluated employing the Kaplan-Meier method with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Adverse events were defined according to Common Terminology Criteria for Adverse Events (CTCAE vs 4.03).

Safety was evaluated descriptively. Diagnosis of acute pancreatitis (AP) was made on the base of the Revised Atlanta Classification: requiring 2 of the following features: (a) characteristic abdominal pain (acute onset, severe character, epigastric pain often radiating to the back), (b) elevated enzyme activity (lipase or amylase) at least 3 times > than the upper limit of normal and (c) characteristic findings on contrast-enhanced CT scan.

3. Results

3.1. Treatment characteristics

We treated a total of 13 pancreatic lesions, comprised of 8 secondary malignancies/ML (61.5%) and 5 primary malignancies: 3 PT (23.1%) and 2 ILR (15.4%). Median diameter of the target lesions was 3 cm (range 1.0–6.5 cm). All lesions were irradiated in a total of 13 sessions with an employed mean of 1.5 catheters (range 1–4). The median administered D100 was 15.3 Gy (range 9.2–25.4 Gy). No OAR were irradiated in excess of critical value during treatment. The median irradiation time was 10.1 min (range 4–33 min).

3.2. Local tumor control, progression free survival and overall survival

Within the median follow up of 6.7 months (range 3.2–55.6 months) 1 patient displayed local recurrence of the GTV, resulting in a LTC of 92.3% in the Kaplan-Meier analysis (Fig. 2). The treated lesion was a ML of gastric squamous cell carcinoma to the pancreatic corpus and was covered with a minimum tumor dose of 12 Gy at time of treatment. Additionally, this patient displayed needle track tumor seeding. Cumulative median PFS was 6.2 months and ranged from 2.8 to 25.7 months, for patients with primary and secondary malignancies PFS was 5.8 (2.9–6.7 months) and 6.2 months (range 2.8–25.7 months), respectively (Fig. 3). Within the follow up period 12/13 patients displayed a systemic progressive disease and out of these 12 patients 7 received specific tumor therapy in the timespan between iBT and systemic progression: in detail, palliative chemotherapy (5/7) and radioembolisation of the liver (2/7). The cumulative median OS was 16.2 months (range 3.3–55.7 months) for patients with primary and secondary malignancies OS was 7.4 (5.8–19.1 months) and 45.6 months (range 3.3–55.7 months), respectively (Fig. 4). At time of censoring 6 patients were still alive (5/8 secondary malignancies). Patient No.4 was

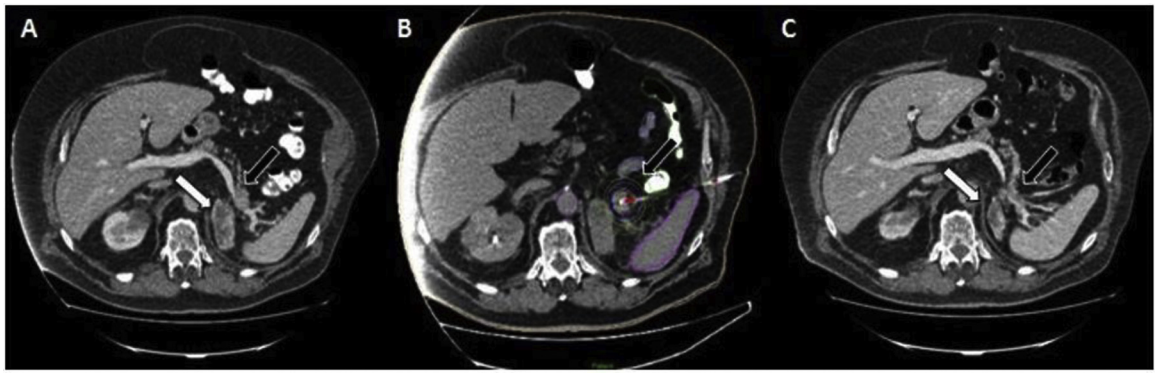

Fig. 1. (A): Pre-interventional contrast-enhanced CT slice showing a metastasis of NCC (black arrow) in the pancreatic tail. White arrow shows a metastasis of NCC of the left adrenal gland, previously treated with high dose rate brachytherapy (HDRBT). (B): Planning CT with indicated CTV (red line), catheter (marked in red) and isodose lines. (C): Follow up after 18 months: local control of treated lesion in the pancreatic tail (black arrow). Size reduction of the previously treated lesion in the left adrenal gland (white arrow).

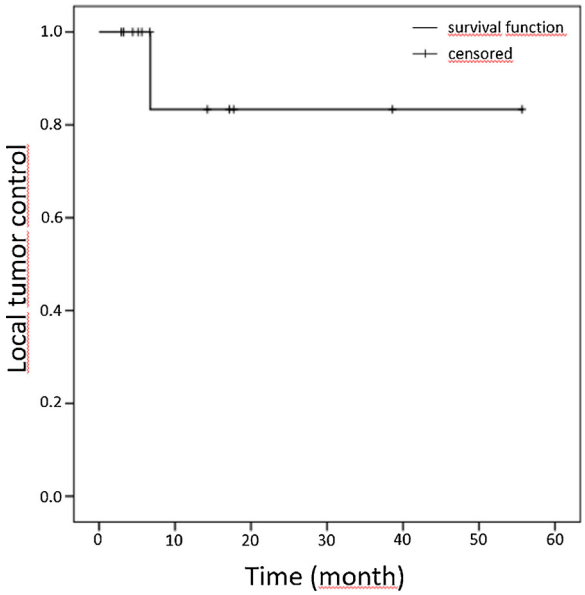

Fig. 2. Local tumor control after iBT of all treated pancreatic neoplasms.

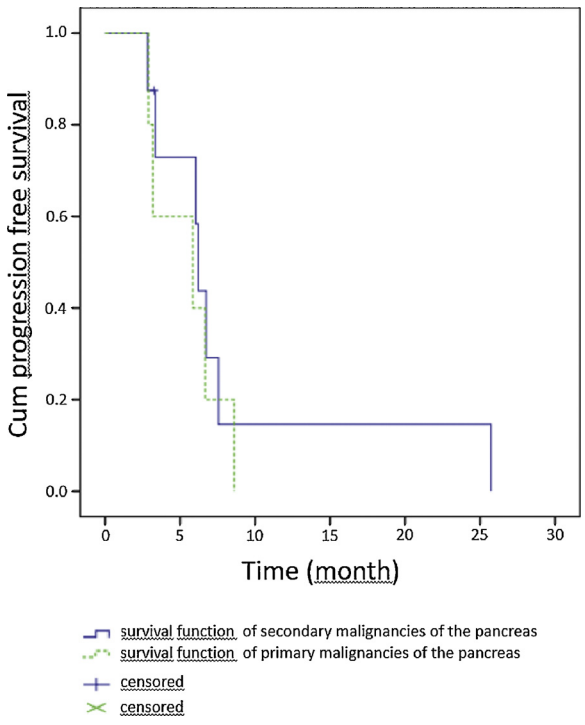

Fig. 3. Progression free survival of patients with primary (green line) and secondary malignancies (blue line) of the pancreas after iBT.

excluded from OS analysis due to lack of detailed information regarding the time point of death.

3.3. Safety and peri-and postinterventional complications

Median hospital stay was 4 days (range 4–11 days), whereby 1 patient underwent catheter positioning twice due to incorrect catheter placement in the first session. Patient No.6 was treated with iBT of the liver in the same hospital stay.

In 1 patient we observed increased level of systemic inflammation markers (C-reactive protein, leukocytosis) without fever or additional symptoms, administration of intravenous antibiotics (Ciproflaxacin and

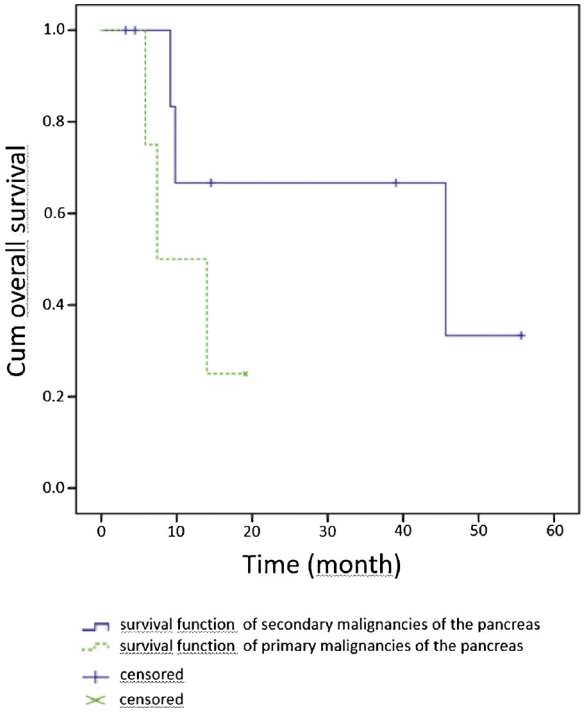

Fig. 4. Overall survival for patients with primary (green line) and secondary malignancies (blue line) of the pancreas after iBT. At the date of censoring 6 patients were still alive.

Metronidazole) led to rapid normalization. 1 patients reported unspecific nausea. With regard to the diagnosis of acute pancreatitis, 2 patients showed biochemical sign of a local injury of the pancreas, i.e. lipase elevated > 3times the upper limit of normal. Patient No.8 additionally experienced characteristic abdominal pain, an ultrasound and CT-scan did not show any sign of bleeding or early phase pancreatitis. The symptoms spontaneously resolved within the hospital stay (7days). However, this event was classified as mild acute pancreatitis, categorized as adverse event grade2. In patient No.9 we also observed critical enzyme elevation, but without any pain and therefore this patient did not received further radiologic examination. In conclusion, after iBT 12/13 patients did not show sufficient clinical features required for the diagnosis of acute pancreatitis on the base of the Revised Atlanta Classification. Furthermore, on the follow-up imaging no morphological features of acute pancreatitis, local complications (in terms of late toxicities) or following structural changes, including pancreatic strictures were observed.

4. Discussion

In selected patients with primary or secondary malignancies of the pancreas surgical resection remains the only possible cure or might achieve long-term survival, respectively [19]. In the literature pancreaticoduodenectomy is described to be associated with a substantial postoperative morbidity of 30–60% and in-hospital mortality rate of fewer than 5% [8,9]. However, Nimptsch et al. analyzed 58,003 inpatient episodes of pancreatic surgery between 2009 and 2013 in Germany and found a overall in-hospital mortality rate of 10.1%, including all surgical procedures of the pancreas; severe surgical complications occurred in 12.2–20.2% (i.e. peritonitis, sepsis, re-laparotomy, and > 6 blood transfusions) [20]. These findings suggest an underestimation of the mortality and morbidity rate due to publication bias, given the fact that low complication rates are mostly reported by single- and multiinstitutional studies of rather experienced hospitals with high caseloads.

However, only a minority of patients diagnosed with pancreatic

neoplasms are candidates for surgery, i.e. less than 20% of the patients diagnosed with PDAC are eligible for resection, likely a result of the tumor's invasiveness and propensity towards metastases [21]. Additionally, even after curative-intent surgery over 60% of patients will develop disease recurrence within 2 years resulting in a dismal prognosis [22], for instance after curative resection plus adjuvant chemotherapy median OS is reported to be 18.7–25 months for PDAC [23,24]. However, after complete pancreatic head resections for PDAC the surgical margin status has significant impact on further treatment an prognosis, with positive microscopic margin status (R1 resection) described to be as high as up to 76% [25]. This fact might explain that ILRs in the remnant pancreas or the locoregional structures are reported to occur in up to 30% after curative pancreatic surgery for PDAC [23,26].

Data is scarce for resection of secondary malignancies, however, Hung et al. found a 5-year survival rate of 61.1% after resection of 241 ML of the pancreas (73.9% renal cell carcinoma), suggesting that pancreatic resection should not be ruled out for ML [27].

In contrast, the presented study provides evidence that iBT achieves a high LTC rate of 92.3% in the ablation of primary and secondary pancreatic neoplasm. Within the median follow-up of 6.7 months 1 patient displayed local recurrence and needle track seeding after iBT of a ML of gastric squamous cell carcinoma, possibly caused by a relatively low administered D100 of 12 Gy regarding the pathologic subtype of the primary tumor.

However, in contrast to the reported surgery associated complication rates our findings demonstrate that iBT is a well-tolerated and safe procedure with no recorded severe adverse events (grade 3+). We report 1 case with mild acute pancreatitis post iBT that spontaneously resolved within 1 week (categorized as adverse event grade2). In the follow-up (including CT or MRI scans) no signs of acute pancreatitis (early or late phase), obstructive pancreatitis due to strictures or other late toxicities to adjacent organs were recorded.

About 30–40% of patients with PDAC are presented with borderline resectable or locally advanced unresectable disease and are -according to the current standard of care- treated with (neoadjuvant/palliative) chemotherapy depending on the patient's performance status [28]. Additionally, for this patient population subsequent local therapies, such as radiofrequency ablation (RFA), microwave ablation (MWA), irreversible electroporation (IRE) and cryoablation are available. These treatments are less evidence based and moreover seen in a palliative context with an emphasis on local tumor control and symptom relief. In general the techniques are delivered via laparotomy, again associated with surgical complications. Furthermore, to our knowledge no data regarding percutaneous ablation of secondary malignancies of the pancreas exists and even literature regarding percutaneous ablation of PDAC or NET is scarce.

RFA is a thermal ablative technique that uses heat generated from high frequency alternating current. The associated risk of thermal injuries to adjacent structures is relatively high, in surgical settings initially resulting in substantial morbidity (up to 40%) and mortality rates (up to 25%) due to massive gastrointestinal bleeding or duodenal injury, after technical adjustments the rates could be lowered to 24–28% and 1.8–3%, respectively [29–31]. To our knowledge, data regarding CT-guided RFA is only reported in cases studies. There are two studies concerning percutaneous, ultrasound-guided RFA, mainly focused on feasibility and safety: D'Onofrio et al treated 18 patients with PDAC with no described postprocedural complications, but efficacy regarding LTC was not assessed [32]; in the second study 7 patients with pancreatic NET were treated with a high complication rate of 3 grade3 adverse events [33]. IBT, in contrast, is independent of technical limitations concerning a potential cooling effect arising from large tumor masses (> 5 cm), resulting in a possible incomplete ablation, and even more importantly implies no potential thermal injury to adjacent OAR.

IRE is a non-thermal technique that uses short pulses of high voltage electrical current to create nanopores in the cell membrane causing apoptosis. In contrast to RFA IRE is thought to be able to destroy tumor tissue without the risk of thermal injuries to adjacent structures. Leen et al included 75 preteated patients with unresectable PDAC, median OS and PFS after CT-guided IRE was 27 and 15 months, respectively; local recurrence was reported to be 3% after 2–3 months [34]. Associated morbidity was 25%, mortality was nil. Although, one of the greatest technical restrictions of IRE is the need for general anesthesia with complete muscular paralysis, which provides additional risk and is a limiting factor for patient selection and procedural setting. IBT in contrast is performed under local anesthesia with analgosedation.

Data regarding percutaneous MWA and cryoablation is scarce and mainly concerning feasibility and safety in small case series [35–37].

Besides resection and percutaneous ablation of pancreatic neoplasms radiotherapy (including conventional radiotherapy and stereotactic bodyradiation = SBRT) provides another non-invasive approach. For patients treated with chemoradiation (gemcitabine plus radiotherapy: 1.8 Gy/fraction for a total of 50.4 Gy) for locally advanced PDAC early grade4 and 5 toxicities are described to occur in 41% and 9%, respectively [38]. SBRT has been studied with varying techniques and radiation doses applied, inducing morbidity rates up to 25% and especially late toxicities (grade2-4) up to 44% [39,40], i.e. adverse effects occurring at least 6 months post radiation of the pancreas, such as gastric/duodenal ulcer or perforation, gastrointestinal bleed, enteritis, colitis, intrapancreatic bile duct stricture. A phase-2-trail showed a LTC rate of 90% over a median follow-up of 13.5 months for 45 patients treated with SBRT for locally advanced PDAC (application of 45 Gy in 6 fractions); median PFS and OS was 8 and 13 months, respectively [41]. 49% of the population experienced grade1-2 toxicities, no grade 3+ events were reported, although, late toxicities occurred in 4% [41]. These results propose that SBRT permits precise irradiation, however, the varying rates for early and late toxicities suggest a significant exposure of normal surrounding tissue, resulting in gastrointestinal complications. Due to its percutaneous delivery iBT in contrast, allows the application of an effective, precise ablative dose in the CTV while saving adjacent OAR from potentially harmful exposure resulting in a low complication rate. Therefore iBT is not limited to the size or restrictions due to anatomic localization of the target. Moreover, in the presented study we did not report any early or late severe toxicities related to iBT.

From an oncological perspective our findings of a median PFS of 6.2 months (range 2.8–25.7 months) and an OS of 45.6 months (range 3.3–55.7 months) after iBT for patients with ML go in line with published outcome after resection. Hung et al, report a median OS of 20.0 months after resection of 241 ML, without the evaluation of LTC and PFS [27], and also Dar et al described a varying survival of 6–56 months for a case series of 5 patients [42]. Since, surgical risk is always one of the major concerns in consideration of any metastasectomy, iBT provides a particularly safe and effective alternative method.

For the patients presented with primary malignancies we found a median PFS of 5.8 months (2.9–6.7 months) and an OS of 7.4 months (5.8–19.1 months), however, our heterogeneous and rather small cohort is not comparable to the existing literature without restrictions, but for patients with locally advanced/unresectable or metastatic PDAC OS is reported to be similar with a median of 4–11 months under 1 st line chemotherapy [43,44]. Therefore, our findings might also suggest a potential additional survival benefit of selected patients treated with iBT, since the oncological impact of any local treatment is far from being answered.

Nevertheless, our study has several limitations: its retrospective nature and the low case number; moreover, the treated cohort was heterogeneous with respect to primary tumor, disease stage and previous treatment, resulting in a PFS and OS that is not beneficial from an oncological perspective. Therefore, a prospective trial with a higher caseload would be needed to investigate the effect of iBT with respect to the primary tumor and the previous treatment and also to possibly establish iBT in the toolbox of local ablative techniques for pancreatic

neoplasms located in the pancreatic body or tail.

However, despite these limitations our study demonstrates that iBT is a feasible alternative to resection of secondary malignancies and also provides a promising treatment for locally advanced/unresectable or recurrent primary malignancies of the pancreas. It offers treatment- and primary-tumor-independent effective LTC rates and accordingly, might offer a well-tolerated therapeutic option in the multidisciplinary management of selected patients.

In conclusion, for patients presented with primary or secondary malignancies of the pancreas located in the pancreatic body or tail iBT is a safe and particularly effective ablative technique that provides a promising alternative to surgery, SBRT and existing percutaneous ablation methods.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Publikation 3

Treatment of metastatic, imatinib refractory, gastrointestinal stroma tumor with image-guided high-dose-rate interstitial brachytherapy.

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BRACHYTHERAPY

Treatment of metastatic, imatinib refractory, gastrointestinal stroma tumor with image-guided high-dose-rate interstitial brachytherapy

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ABSTRACT

PURPOSE: Evaluation of efficacy and safety of CT- or MRI-guided high-dose-rate interstitial brachytherapy (iBT) in the treatment of advanced, imatinib refractory, metastatic gastrointestinal stroma tumors (GISTs) was the objective of this retrospective study.

METHODS AND MATERIALS: A cumulative number of 40 unresectable metastases (30 hepatic, 10 peritoneal) were treated with iBT in 10 selected patients with histologically proven GISTs. Six patients had peritoneal disease, and 5 patients were even progressing under sunitinib (second line)—thus iBT was applied as a salvage maneuver. IBT uses an interstitially introduced ^{192}iridium source in a high-dose-rate irradiation regime to destroy vital cells in a single fraction. Response to treatment was assessed clinically and with acquisition of MRI/CT every 3 months.

RESULTS: Local tumor control was reached in 97.5% of all treated metastases during a median time of 25 months—only one local relapse was observed during followup. The median diameter of the irradiated lesions was 2.4 cm (range 0.6−11.2 cm); a median dose of 15 Gy (range 6.7−21.96 Gy) was applied. The median progression-free survival after iBT was 6.8 (range 3.0−20.2) months; the median overall survival was 37.3 months (range 11.4−89.7). Two major complications (Common Terminology for Adverse Events grade 3) occurred following the intervention: local hemorrhage and pneumothorax, successfully dealt with by angiographic embolization and pleural drainage, respectively.

CONCLUSIONS: In selected patients with metastatic, imatinib refractory GISTs, iBT safely enables high rates of local tumor control and presents an alternative, anti-neoplastic treatment option even in a salvage situation.

Keywords: GIST; Interstitial brachytherapy; Local ablation; Local tumor control; Salvage; TKI resistance

Introduction

Gastrointestinal stroma tumors (GISTs) are the most common type of mesenchymal tumors in the gastrointestinal tract with a yearly incidence of 1−2/100000 and account for 1−3% of all GI tract neoplasms, following gastric and colorectal cancer (1). GISTs arise from the interstitial cells of Cajal in the lamina muscularis mucosae, which physiologically function as pacemakers of the gastrointestinal motility. Reported incidences of distant metastases from GISTs ranges between 23% and 47%, thereof 20−60% in the liver; 50% of these patients have peritoneal disease (2,3). About 15−20% of patients with GIST have metastatic disease at diagnosis.

Overactivation or gain-of-function mutations in the KIT and PDGFRA genes, which code for tyrosine kinase receptors, are responsible for proliferation and survival of GIST tumor cells. According to a gene analysis study, KIT mutations occur in 75−80% and PDGFRA mutations in 7% of patients (4). GISTs without the aforementioned mutations are referred to as wild-type malignancies and account for

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about 15% of these tumors. Since its introduction, the tyrosine kinase inhibitor (TKI) imatinib serves as the backbone of metastatic GIST therapy—up to 80% of patients show an initial response to treatment (5,6). Mutations of a KIT exon 11 have been demonstrated to be associated with better progression free survival (PFS) and overall survival (OS) than mutations of KIT exon nine or wild-type GISTs. (7) KIT exon nine mutations have been identified as the most important adverse prognostic factor for risk of progression and death. (7) Resistance to imatinib is often a result of secondary gene mutations, developed typically 18−24 months after initial successful systemic therapy in more than 50% of all cases. Therefore, the median time of recurrence is around 2 years. Primary TKI resistance is defined as the evidence of disease progression during the first 6 months of imatinib treatment, and secondary resistance is defined as tumor progression after 6 months of initial tumor response or stable disease. Before treatment with TKI agents, the prognosis for patients with metastatic GIST was poor with a median overall survival of less than 2 years (8). The OS for limited metastatic GISTs under imatinib treatment has been described in different trials; a median overall survival of 57, 53, and 45 months was reported in three studies (9).

Although international guidelines currently do not primarily recommend a surgical approach for extensive metastatic GISTs, the combination of systemic therapy (Imatinib) with metastasis resection shows a tendency to prolong survival in highly selected patients. (10) In cases of limited metastatic disease, guidelines suggest treatment of progressing lesions with resection or ablation while continuing systemic TKI treatment. (7) However, evidence based on prospective, randomized trials with unselected patients is still lacking. Besides, few patients are prospects for surgery because of tumor dissemination or general condition/comorbidities.

Radiofrequency ablation (RFA), either intraoperative or transcutaneous, is an alternative method to achieve tumor control, which had been applied to other tumor entities and was evaluated for patients with hepatic GIST metastases by a few reports with a low number of patients. (2,11,12).

An alternative local ablative measure to RFA is interstitial brachytherapy (iBT), which is based on the application of internal radiation in contrast to thermal ablation methods like RFA. IBT employs ^{192}Iridium, a highly active, gamma-radiation emitting radionuclide, which is transiently installed inside the target lesion. CT- or MRI-guided iBT has been proven to be a safe and effective procedure to treat primary or secondary liver and extrahepatic tumor entities by several investigators in the past. (13−16).

To our knowledge, no study has assessed the efficacy of image-guided high-dose-rate (HDR) iBT in the treatment of metastatic GISTs. The purpose of this retrospective study was to evaluate safety and efficacy of iBT application for the treatment of metastatic GISTs in a collective of 10 patients with 40 GIST metastases.

Methods and materials

Patient characteristics

Ten patients with histologically proven GISTs and a cumulative number of 40 unresectable metastases received treatment with iBT in our department between August 2009 and February 2016 and were enrolled in our retrospective study. Every patient was in a metastatic and progressive stage of disease at the time of referral to our department. Our study was approved by the local ethics committee.

Study design and eligibility criteria

Local tumor control (LTC) was the primary endpoint of this retrospective study; overall safety of iBT was the secondary endpoint.

Each individual patient's case with GIST was discussed at an interdisciplinary board of oncologists, interventional radiologists, and visceral surgeons who determined the indication for iBT for each patient individually.

The inclusion criteria were (1) resection impossible or unfavorable because of risk or (in case of liver metastases) loss of liver function, (2) patient unwilling to undergo surgery, (3) oligometastatic/controllable disease extent ($\leq$5 metastatic lesions on initial investigation), and (4) adequate coagulation parameters (thrombocytes $>$ 50000/nl, prothrombin $>$50%, partial thromboplastin time $<$ 50 s). Exclusion criteria were correspondingly (1) lack of consent and (2) uncontrollable tumor spread.

Interventional technique and irradiation

Preliminaries

Before the local ablation procedure took place, a whole-body contrast enhanced CT, and in case of hepatic tumor involvement, a Gb-EOB-DTPA−enhanced MRI (Primovist, Bayer Pharma, Leverkusen, Germany) was acquired for staging and treatment planning purposes. Laboratory parameters and physical status were checked preintervention with iBT.

Procedure

In a first step, local anesthesia (lidocaine) as well as intravenous analgesia (fentanyl) and sedation (midazolam) were administered, adapted to the individual weight, discomfort, and pain level of each patient. In the next step, the target lesions were punctured using an 18-gauge needle under CT-fluoroscopic guidance (Toshiba, Aquilion, Japan) or real time 1.0 T MRI (Panorama 1.0 T, open MR system, Philips Healthcare). After this, a flexible 6-french catheter sheath (Radifocus, Terumo, Tokyo, Japan) was placed applying the Seldinger's technique over a stiff angiography guidewire (Amplatz, Boston Scientific, Marlborough, USA). In a last step, the 6-french afterloading catheter (Afterloadingkatheter, Primed Medizintechnik Gmbh,

Halberstadt, Germany) was introduced, and the extracorporal catheter ending transiently fixated to the skin with a cutaneous suture and sterile bandages. The angulation and number of catheters were determined individually in consideration of organs at risk in close proximity and target lesion size. Finally, to confirm correct catheter positioning and to plan the following irradiation, a CT scan in breath-holding technique or a gadolinium-enhanced MRI was acquired. The clinical target volume (CTV) and the adjacent organs at risk (e.g. gastrointestinal tract) were highlighted by the interventional radiologist in every CT or MRI slice.

Irradiation design and dosimetric analysis

Design

Detailed and individual treatment strategy was planned using the acquired data set and the software system Oncentra (Nucletron, Elekta Ab, Stockholm, Sweden), an integral part of the HDR-afterloading system. The three-dimensional coordinates (x, y, z) of each inserted catheter's tip and exit at the tumor margin were determined and transferred into the treatment planning system. The calculated isodose lines were controlled in every slice and if necessary adjusted depending on the target lesion margins. Each target lesion's boundary was established individually for every inserted catheter. An example of the interventional technique is illustrated in Fig. 1.

Irradiation

The HDR brachytherapy/afterloading system (Nucletron, Elekta Ab, Stockholm, Sweden) applied an ^{192}Iridium source with a nominal activity of 10 Ci or 370 GBq, which was administered as a single fraction irradiation. The applied reference dose of 12 Gy was defined as the anticipated minimum dose to enclose the target lesion entirely and was installed in a single fraction. Even higher doses were possible and certain at the tumor center. A security margin of 5 mm surrounding the target lesion defining the CTV was incorporated to prevent new peripheral tumor incidences. Before radiation planning, the inserted brachytherapy catheters are fixated to the skin; hence, they maintain position and stay intratumoral even during body movement or respiration; therefore, in this case, PTV is equal to CTV. Organs at risk, such as the proximal gastrointestinal tract (empiric dose $<$ 14 Gy/mL), (17) in close proximity to the target lesions were taken into consideration and the irradiation dose correspondingly adjusted.

Catheter removal

Finally, after the irradiation was completed, the catheters were removed, and the punctures sites sealed by insertion of gelfoam or injection of fibrin tissue glue. Patients stayed

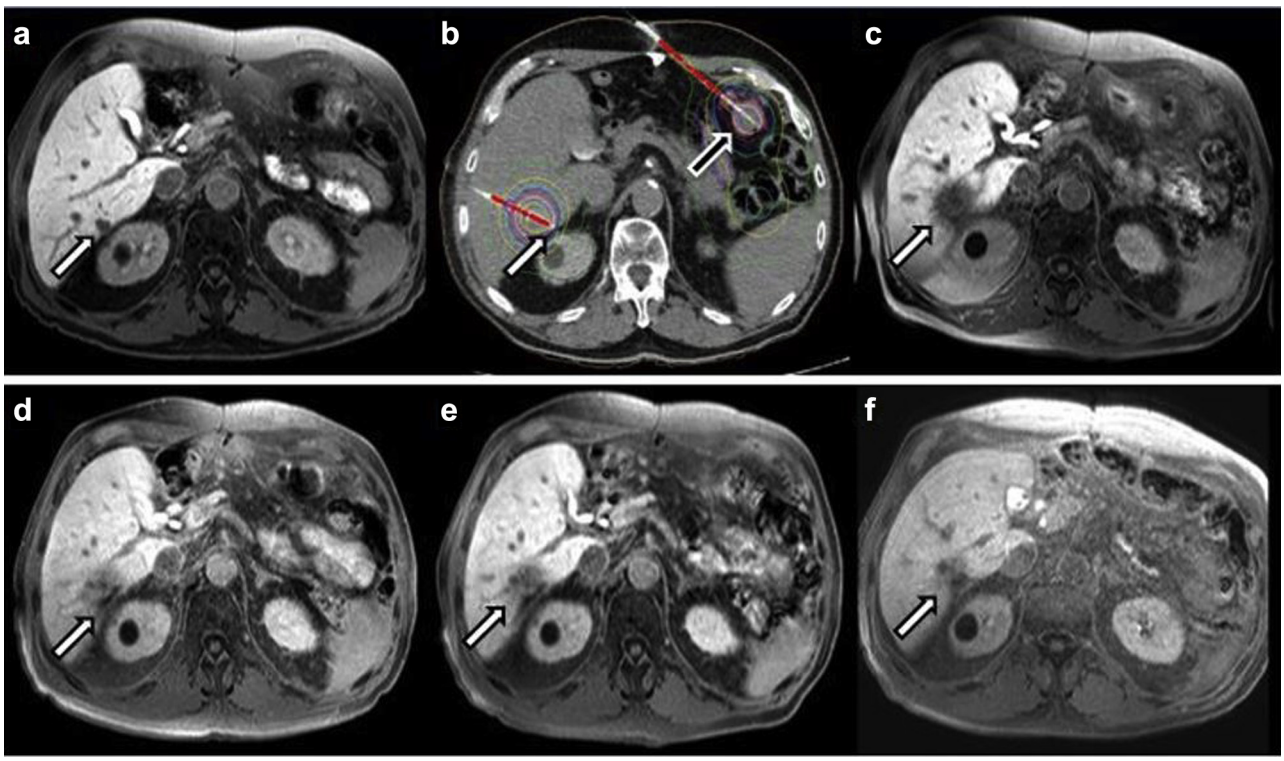

Fig. 1. (a): Baseline Gd-EOB-DTPA enhanced T1w MRI. White arrow indicates gastrointestinal stroma tumor metastasis in liver segment 6. (b) Demonstrates inserted brachytherapy catheters in the liver lesion (white arrow) and in a second extrahepatic peritoneal lesion (black arrow). Lines represent isodoses with red line showing 12 Gy. (c−f): Followup and local control documentation of hepatic lesion 3 (c), 6 (d), 9 (e), and 30 (f) months after iBT. Note the Gd-EOB-DTPA enhancement defect (dark rim around lesion) after iBT in (c) and recovery in (d-f). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

in our postinterventional observation unit for a short period of time before transfer to the ward.

Followup

Schedule

Evaluation of response to iBT treatment was done every 3 months after local ablation procedure; a contrast-enhanced whole-body CT and a Gb-EOB-DTPA−enhanced liver MRI in case of liver involvement as well as a clinical and laboratory checkup were performed.

Adverse events

Potential adverse events associated with the local therapy were recorded and defined corresponding to the "Common Terminology for Adverse Events" (CTCAE) version 4.03 and according to the guidelines of the Society of Interventional Radiology (18).

Definitions of local tumor control rates (primary endpoint) and remission criteria

Definition

LTC after brachytherapy was defined corresponding to the Choi Criteria for GISTs categories as stable disease, partial remission, and complete remission. An increase in diameter >20% during followup was deemed to be progressive disease.

Pitfalls

Assessment of tumor response in routine followup examinations had to be done meticulously because of two crucial factors: (1) radiation hepatitis can often mimic tumor growth, (2) GIST metastases not only change in size but also in density; a typical described progression pattern addressed in the Choi criteria is a lesion becoming partially hyperdense ("nodule within the mass").

Statistical methods

The study was retrospective. Local tumor control as primary endpoint and OS as well as progression-free survival were calculated (from the time of each patient's first local therapy) by employment of the Kaplan−Meier method with SPSS version 22 (SPSS, version 22.0, SPSS, Chicago, Illinois). The secondary endpoint, safety, was evaluated descriptively.

Results

Ten patients with histologically proven GISTs were treated with iBT in our institution between August 2009 and February 2016. The median patient age at the time of diagnosis was 58.5 (range 37−68) years with a male to female ratio of 9:1 (Table 1).

The primary GIST site was six in the stomach, three in the small intestines, and one in the rectum. The mutational status of our patients is unknown; no genetic analysis has been performed. Eight patients had resection of the primary before referral to our institute. Recurrence operation, partial hepatectomy, and whipple operation were performed in 1 patient each. Before the local treatment, every patient underwent the first line therapy with imatinib. Five patients

Table 1
Patient characteristics

Total number of patients	10
Patient sex	
Men	9
Women	1
Age at time of diagnosis	
Median	58.5
Range	37−68
Primary tumor localization	
Stomach	6
Small intestines	3
Rectum	1
Metastases (cumulative)	
Liver	30
Peritoneal	10
Metastases timeframe	
Metachronous	6
Synchronous	4
Lesion size (cm)	
Median	2.4 (Q_1 = 1.5, Q_3 = 3.7)
Range	0.6−11.2
Irradiation dose (iBT) (Gy)	
Median	15.0 (Q_1 = 12.2, Q_3 = 16.4)
Range	6.7−22.0
Irradiation time (iBT) (min)	
Median	28.5 (Q_1 = 17.5, Q_3 = 40.3)
Range	2.3−69.3
Number of catheters/lesion	
Median	1
Range	1−11
Local tumor control (LTC)	39/40 (97.5%)
Median time (month)	25
Followup time (month)	
Median	24.6 (Q_1 = 7.9, Q_3 = 41.1)
Range	2.3−92.9
Time to progression (month)	
Median	6.8 (Q_1 = 5.5, Q_3 = 8.0)
Range	3.0−20.2
Overall survival after iBT (month)	
Median	37.3 (Q_1 = 20.6, Q_3 = 47.3)
Range	11.4−89.7
OS from time of diagnosis (month)	
Median	107 (Q_1 = 65.8, Q_3 = 160.3)
Range	41−203
Previous treatment (before iBT)	
First line (Imatinib)	10 (100%)
Second line (Sunitinib)	5 (50%)
Resection	8 (80%)
iBT image guidance	
CT	34
MRI	6
Time of hospitalization (days)	
Median	4
Range	3−6

received second line therapy with sunitinib. TKI systemic therapy was continued in 7 patients after the local therapy and before disease progression.

Treatment characteristics

The locations of GIST metastases were as follows: 30 hepatic and 10 peritoneal. Most patients' metastases were treated in several iBT sessions (an overview is given in table 2). The median target lesion diameter was 2.4 cm (range 0.6−11.2). CT guidance was used in 34 interventions, and MRI guidance was used in 6. A median of one (n = 1) catheter was placed into each tumor (range 1−11 catheters). The prescribed minimal tumor reference dose was 12 Gy. In some cases, the nominal dose had to be adjusted because of tumor size or proximity of organs at risk, which led to a median applied dose of 15.0 (range 6.7−22.0 Gy). Total irradiation time varied between 2.3 and 69.3 min with a median of 28.5 min. The time of hospitalization ranged from 3 to 6 days with a median of 4 days. Two patients experienced a major adverse event (CTCAE grade 3): local hepatic hemorrhage, which was dealt with successfully by embolization in digital subtraction angiography and prolonged hospitalization (4 days); pneumothorax, which required a pleural drain. The location of the treated tumor in the single case of pneumothorax was liver segment VIII, and because of the pericapsular locus, a needle forerun was needed to minimize the risk of potential liver hematoma. Furthermore, the access was impeded by a deep sulcus/recessus, which was punctured during catheter placement resulting in a pneumothorax.

Elevated inflammatory parameters (CTCAE grade 1) were observed in 3 patients, who consequently received postinterventional antibiotics; no sign of abscess or any other focus in imaging or followup examinations was seen. One patient was given antibiotics as a precaution; no sign of infection was detected after iBT.

Local tumor control, overall survival, progression-free survival

LTC was achieved in 97.5% of all treated lesions over a median time of 25 months in the Kaplan−Meier analysis; only one relapse was noticed during followup (Fig. 2). The median progression-free survival was 6.8 (range 3.0−20.2) months (Fig. 3), and the median overall survival 37.3 (range 11.4−89.7) months (Fig. 4). The current OS status of all patients with GIST in the collective: 6 dead and 4 alive.

Table 2
iBT intervention overview

Patient	Number of iBT interventions	Treated metastases	Time interval between iBTs (months)
1	2	1/2	10
2	3	1/1/1	8/4
3	2	1/2	9
4	3	1/1/1	0,5/1
5	2	1/3	0,5
6	6	3/1/2/2/3/2	22/17/15/15/0,5
7	1	1	-
8	2	1/1	7
9	2	1/3	4
10	2	2/1	1

Discussion

The treatment of metastatic GISTs remains challenging to this date, especially in the case of hepatic involvement or peritoneal disease, which are the most common sites of relapse occurrences (19). International guidelines like European Society for Medical Oncology and National Comprehensive Cancer Network (NCCN) from 2018 differentiate between widespread and limited progressive disease. (7,20) TKI dose escalation and change of therapeutic regimen (second line) with an imaging followup to reassess treatment response and evaluate further options are recommended for widespread progression. However, for metastatic GISTs that show limited disease progression, a more aggressive approach is suggested (NCCN, European Society for Medical Oncology); TKI should be continued, and progressing lesions should be considered for treatment with resection, RFA, or (chemo) embolization. In the case of even further disease progression despite imatinib or sunitinib, regorafenib treatment or other options like antineoplastic agents or clinical trials can be attempted.

The role of surgery in metastatic or recurrent disease is controversial, and meticulous case selection is crucial. The potential benefit is difficult to anticipate and quantify. Raut *et al.*, some of the first investigators to publish results of surgically treated metastatic GISTs in the imatinib era,

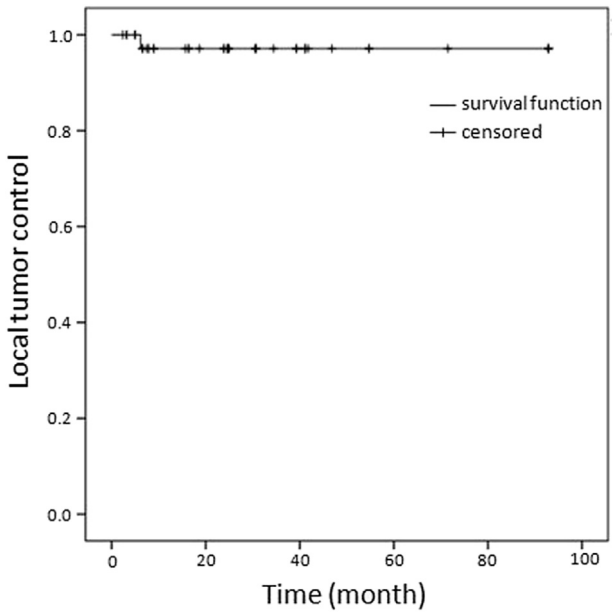

Fig. 2. Local tumor control after iBT of gastrointestinal stroma tumor metastases.

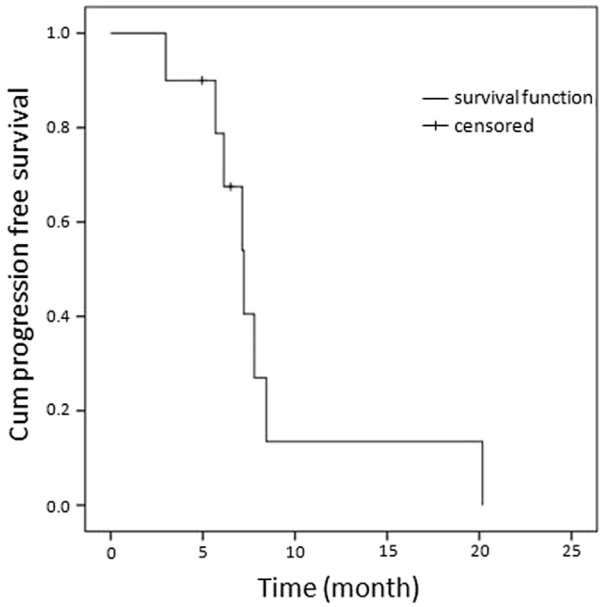

Fig. 3. Progression-free survival (calculated from the time of iBT) of patients with metastatic gastrointestinal stroma tumor after treatment with iBT.

reported an OS of 29.8 months and a median PFS of 7.7 months for patients with limited disease progression (n = 32). (21) Similar, subsequent, retrospective studies confirmed those observations. The EORTC-STBSG collaborative study (n = 239), the largest series of patients treated at high-volume centers in Europe, with different disease extent patients groups reported a median OS of 1.5 years from time of metastasectomy in the patient group progressing at the time of surgery (22).

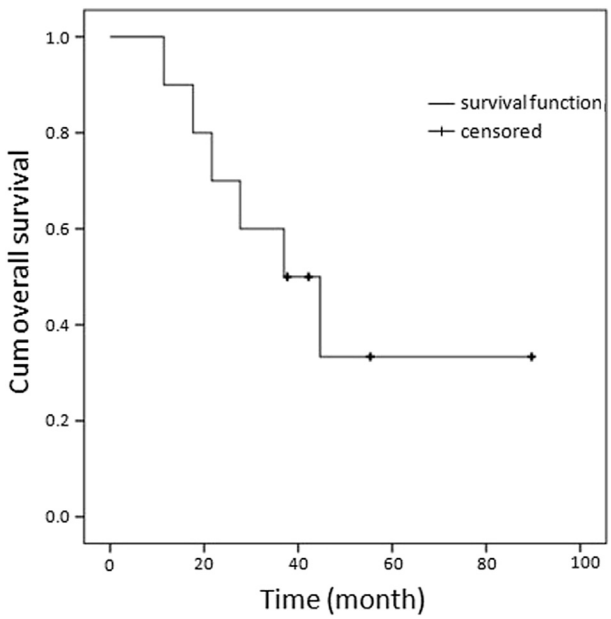

Fig. 4. Graph shows overall survival (calculated from the time of iBT) of patients with metastatic gastrointestinal stroma tumor ablated with iBT.

If complete resection is not feasible, one main goal and indication of either local ablation or surgery in a limited progression setting refractory to imatinib is to minimize tumor clone selection with secondary mutations, which otherwise cements TKI resistance and consequently hinders further systemic treatment. The greater the number of tumor cells exposed to TKI treatment and the higher the tumor growth rate (mitotic counts), the higher the chance of molecular evolution and secondary TKI resistance. Secondary TKI resistance following tumor clone outgrowth and selection is one of the major difficulties in metastatic GIST treatment. Xia et al. came to the conclusion that patients with poor imatinib response show improved survival after resection of liver metastases and reported a 3-year survival rate of 89.5%, indicating a benefit of cytoreduction. (23) However, intra-/perioperative tumor rupture bears a considerable risk of tumor cell spillage into the peritoneal cavity and consecutive potential for development of peritoneal carcinomatosis. Furthermore, the NCCN guidelines point out that incomplete resections (R1 or even R2) are frequent and complication rates are high; therefore, careful selection of eligible patients is advised. Finally, the lack of any randomized, prospective data precludes an unequivocal or general recommendation for surgery.

Local ablation therapy, however, presents a promising and alternative treatment option, applicable as a standalone measure or combined with surgery. In the study by Sun Yoon *et al.,* combined intraoperative RFA with surgery in highly selected patients, resecting large lesions and carefully ablating smaller ones to preserve as much liver function as possible; (19) 24 patients were treated with intraoperative RFA; 5-year OS rate of 87.7% and two major complications (biliary stricture and hepatic abscess) were reported. The high survival and low recurrence rates of that study have been attributed to the highly selected patient cohort: RFA inclusion criteria with a tumor size <3 cm, an exact intraoperative positioning and the pre and postoperative imatinib therapy. Pawlik *et al.* treated metastatic GISTs with intraoperative radiofrequency ablation and reported a median OS of 47.2 months. (24).

In contrast to RFA, the application of iBT to metastatic GISTs as an internal, high-dose single fraction radiation method has not been explored so far. IBT has been tested and validated on different primary and secondary liver tumor entities by few researchers in the past (13,15,16). Liver malignancies originating from hepatocellular carcinoma and colorectal cancer were some of the first entities treated with iBT; local tumor control rates of 95% and 88% after 12 months were reported.

Corresponding to these figures, the results of our study (Figs. 2–4, Table 1) demonstrate a high local tumor control rate of 97.5% over a median time of 25 months, a mOS of 37 months, and a PFS of 6.8 months (calculated after iBT) for our patients despite being in an advanced, progressive stage. Median OS from the time of GIST diagnosis was 107 months; at that time 4 patients already had synchronous

metastases. Half of our patients were even progressing while receiving second line therapy (sunitinib) and 6 of 10 patients had peritoneal disease; thus iBT was applied as a salvage maneuver with the intention to delay further progression. Demetri *et al.* demonstrated in a randomized controlled trial that the median PFS for patients with imatinib-refractory metastatic GISTs treated with sunitinib is 24.6 weeks. (25) In summary, taking the salvage situation of our patient collective into consideration, the OS and PFS results are at least similar or even better than those of comparable surgical or RFA data.

In contrast to the rather conventional, external fractionated EBRT, whose role is currently limited to rare cases of GIST bone metastasis according to guidelines, brachytherapy applies a highly active ^{192}Iridium radionuclide to metastatic lesions internally. It decays by emitting gamma (γ) radiation at an activity of around 10 Ci or 370 GBq. Commonly known restrictions of thermal ablation measures like RFA do not apply to brachytherapy. There are no general limits to tumor size, no cooling effects from nearby vessels, and fewer restrictions concerning adjacent risk structures. The issue of potential needle-track metastasis was addressed specifically by radiation of the interventional access as a precaution.

The occurrence and severity of peri and postinterventional complications were low. Two major adverse events (Grade 3), a local hepatic hemorrhage treated with embolization and a pneumothorax requiring a pleural drain, were recorded. Time of hospitalization was not overly prolonged in these cases; both patients stayed in our ward for 4 days. According to literature, major adverse events (Grade 3 and 4) after iBT are observed in 3% of cases and are usually dealt with by angiographic embolization in case of active hemorrhage. (26,27) In comparison, a prospective cohort study, where cytoreductive surgery was performed on patients with sunitinib therapy, 15% of patients experienced a major complication (Grade III). (28).

Short term, postinterventional hospitalization was a safety precaution to monitor potential and occult hemorrhage or other side effects. Patients could usually be discharged after 48 h.

TKI therapy after iBT was discontinued in 3 patients for unknown reasons. Besides, duration of TKI administration after local therapy is also unknown in our patient collective. Early TKI cancellation at any given time is known to bear a high risk of recurrences and certainly has a significant impact on PFS and OS. (29).

Limitations of this study, equal to other data assessing different therapeutic options for metastatic GISTs, are the low patient number and the retrospective nature. The lack of genetic analysis and therefore missing mutational status was considered another limitation. However, recent research indicates that, contrary to general expectation, mutational status does not have a significant prognostic influence concerning a surgical or local ablative approach; (30) cytoreduction through surgery or ablation is assumed to have a countering effect on the negative impact of KIT exon nine mutations. Nevertheless, the potential gain of cytoreduction for TKI refractory patients is still far from understood.

There is an urgent need for a prospective randomized trial with a large patient collective and a control group to validate promising therapeutic options for metastatic GISTs like brachytherapy.

The success of local ablation methods in selected patients in general should be considered an incentive for wider application. Patients with metastatic GIST, especially those who are not eligible for extensive surgery, might benefit particularly not only because of direct cytoreduction but also because of lower risk of tumor clone selection and development of secondary TKI resistance.

Conclusion

The results of our study confirm the overall safety of the image-guided HDR iBT procedure. This local ablation method enables excellent rates of local tumor control for metastatic GIST lesions—even in a salvage situation—and indicates prolonged survival in selected patients ineligible for surgery.

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Publikation 4

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.

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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-

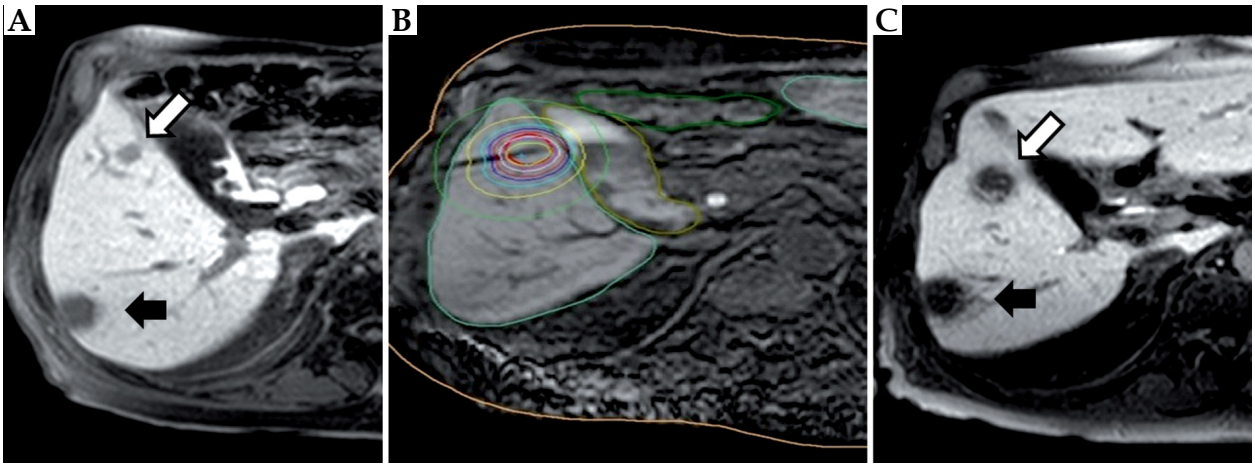

Fig. 1. A) Gd-EOB-DTPA enhanced T1w MRI of a patient with liver metastasis from esophageal squamous cell carcinoma and sequential treatment with interstitial high-dose-rate brachytherapy (HDR IBT = IBT). White arrow indicates lesion planned for IBT and black arrow shows characteristic Gd-EOB-DTPA enhancement 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

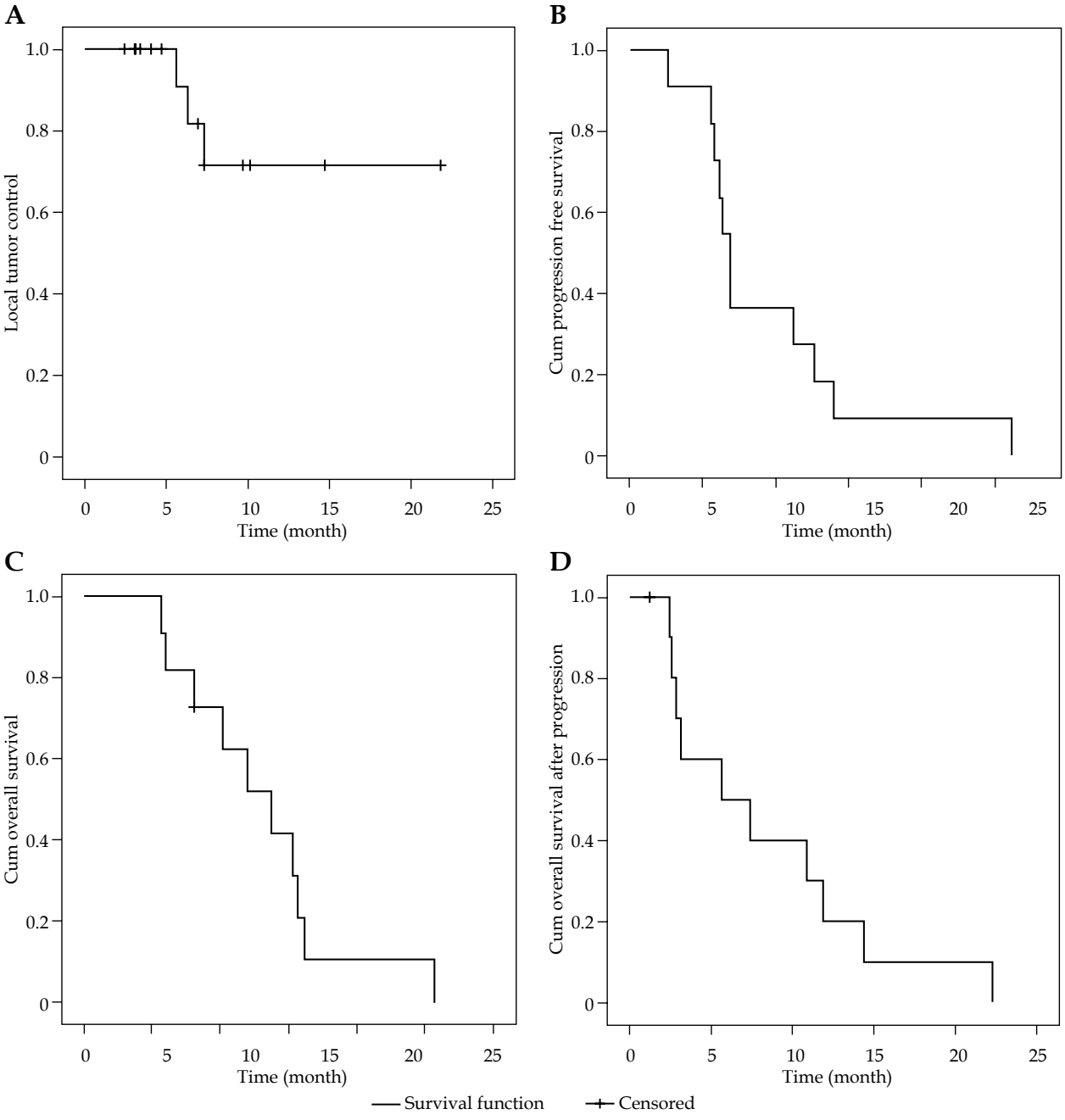

Fig. 2. Kaplan-Meier curves show **A)** local tumor control and **B)** progression-free survival of patients with squamous cell carcinoma metastases ablated with interstitial high-dose-rate brachytherapy. Overall survival and overall survival after tumor progression of the same patients is depicted in **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.

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Publikation 5

Treatment of metastatic gastric adenocarcinoma with image-guided high-dose rate, interstitial brachytherapy as second-line or salvage therapy

Omari J, Drewes, R. Othmer M, Hass P, Ricke J, Pech M, Powerski M.

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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Treatment of metastatic gastric adenocarcinoma with image-guided high-dose rate, interstitial brachytherapy as second-line or salvage therapy

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Ralph Drewes
Max Othmer
Peter Hass
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PURPOSE
We aimed to evaluate the safety and effectiveness of image-guided high-dose rate interstitial brachytherapy (iBT) for the treatment of patients with hepatic, lymphatic, and pancreatic metastases originating from gastric cancer, an entity rarely surgically treatable with curative intent.

METHODS
Twelve patients with a cumulative number of 36 metastases (29 liver, 2 pancreatic, 5 lymph node) from histologically proven gastric adenocarcinoma received iBT between 2010 and 2016 and were retrospectively analyzed. Every patient underwent palliative chemotherapy prior to iBT. The iBT procedure employs a temporarily, intratumorally placed iridium-192 source in a single fraction with the goal of tumor cell eradication. Effectiveness was assessed clinically and by radiologic imaging every three months.

RESULTS
Local tumor control was achieved in 32 of all treated metastases (89%). Four lesions showed a local recurrence after 7 months. Lesion sizes varied from 9 to 102 mm with a median of 20 mm. The median progression-free survival was 6.6 months (range, 1.8–46.8 months). The median overall survival was 11.4 months (range, 5–47 months). One patient suffered a major complication following iBT, hepatic hematoma and abscess (Common Terminology Criteria for Adverse Events grade 3), successfully dealt with by transcutaneous drainage.

CONCLUSION
iBT is an overall safe procedure, which facilitates high rates of local tumor control in treatment of metastatic gastric adenocarcinoma. Compared with surgical metastasectomy, similar overall survival rates could be achieved in our patient collective after iBT application.

Although a constant decline of general gastric cancer incidence has been observed in the past decades, which is assumed to be the result of higher standards in hygiene, nutrition, and *Helicobacter pylori* eradication, this disease still remains the second cause of cancer-related death of all malignancies worldwide (1, 2). The incidence of advanced stage diagnoses has risen in the past 20 years and gastric cancer detected at a stage >T1N0 has a poor prognosis; about two thirds of all patients already have an advanced primary tumor or even present with metastases at the time of diagnosis (2). During the course of the disease the incidence of hepatic metastases varies between 30% and 50% in Western Europe (3, 4). At the time of diagnosis 4%–14% of patients have metastatic liver manifestations and evidence of distant metastases in general is found in 35% of patients (5, 6). Metachronous metastases after execution of curative gastrectomy are observed in up to 25%–30% of patients, 80% of which emerge within the first two postoperative years. Surgical resection with D2 lymphadenectomy remains the gold standard in gastric cancer therapy with curative intention (7). Median survival in cases of metastatic gastric cancer without treatment is reported to be around 3–5 months (8). Palliative chemotherapy can improve survival to about 11 months, with application of anti HER2 treatment and second-line chemotherapy up to 13 months (9).

Surgical treatment is rarely performed in metastatic disease due to lack of evidence of increased survival time; randomized prospective studies such as the Renaissance / FLOT 5

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study and the GASTRIPEC study will have to demonstrate the value of aggressive surgical therapy. The AIO-FLOT3 study, although not randomized, as well as several retrospective studies already indicated improved survival in surgically treated oligometastatic gastric cancer (10). A recently published systematic review and meta-analysis of 39 studies and 991 patients by Markar et al. (11) also concluded a significantly prolonged survival in surgically treated liver metastasis. The European Society for Medical Oncology (ESMO) guidelines currently do not recommend resection in a metastatic disease stage (12).

Very few studies evaluate the significance of local-ablative measures like radiofrequency ablation (RFA) or iBT concerning liver metastasis of gastric adenocarcinoma (13–15). Retrospective studies suggest similar improvements in median survival comparing RFA and surgical treatment (13, 14). One study by Geisel et al. examines the use of iBT for treatment of hepatic metastases from gastric or gastroesophageal adenocarcinoma in 8 patients (16). The main limitation of those studies is the low number of patients.

The effectiveness of iBT has been demonstrated for different carcinoma entities or types of primary and secondary liver malignancies by several investigators (17–20). A major advantage of iBT is its wide range of applicability in almost every imaginable site/organ like pancreas, lymph nodes, adrenal glands, lungs and so on, as demonstrated by researchers like Mohnike et al. and Wieners et al. (21, 22). One or several catheters are placed into the target lesion and an iridium-192 source is installed for the single fraction irradiation. During iBT, a method which has fewer restrictions than thermal ablation measures like RFA, the typical high tumor enclosing reference dose of 20 Gy is applied at the tumor margin and even higher doses at the tumor center to destruct vital tumor cells.

The purpose of this retrospective study was to evaluate the safety and effectiveness of iBT concerning treatment of metastases from advanced stage gastric cancer.

Main points

- Overall survival of metastatic gastric adenocarcinoma is poor and treatment is challenging.
- No treatment consensus has been reached for metastatic gastric cancer.
- Both gastrectomy and metastasectomy are considered experimental in metastatic disease from gastric cancer, as prospective, randomized data are still lacking.
- Interstitial, image-guided brachytherapy (iBT) presents an alternative, overall safe treatment option to inactivate metastatic tumor cells by DNA and RNA damage.
- In selected patients, iBT enables high rates of local tumor control and facilitates prolonged survival in second-line and salvage treatment settings.

Methods

Study design and eligibility criteria

The primary endpoint of this retrospective study was local tumor control; the secondary endpoint was the overall safety of the local ablation method iBT. An interdisciplinary consensus comprised of oncologists, visceral surgeons and interventional radiologists established the indication for iBT in each individual case. The inclusion criteria were determined to be as follows: 1) resection deemed unfavorable due to accessibility, risk/invasiveness, comorbidities and the corresponding ramifications concerning preservation of liver function and tissue due to security margins; 2) adequate coagulation (thrombocytes >50000/nL, prothrombin >50%, partial thromboplastin time <50 s) and liver (bilirubin <30 µmol/L) parameters; 3) oligometastatic disease (≤5 metastases upon initial presentation) and no disseminated metastases; 4) lack of patient consent for surgery. Exclusion criteria were an extensive and uncontrollable tumor spread and peritoneal carcinomatosis in particular. All patients have given their informed consent to participate in the study. The study has been approved by the local ethics committee.

Interventional technique and irradiation

Prior to the scheduled intervention with iBT, a whole-body contrast-enhanced computed tomography (CT) examination and in case of liver metastases an additional gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gb-EOB-DTPA) enhanced magnetic resonance imaging (MRI) was acquired for planning and re-staging purposes. Furthermore, every patient had to pass a thorough clinical check-up and a physical examination; current laboratory parameters were needed as well, before the go-ahead was ultimately given.

Following local anesthesia (lidocaine), peri-interventional sedation (midazolam) and analgesia (fentanyl) adapted to individual discomfort or pain level each patient had to endure during the intervention, one or several percutaneous catheters were implanted intratumorally into the target lesion. Puncture of the lesions was performed using an 18-gauge needle under CT-fluoroscopic guidance (Toshiba). Afterwards, the puncture needle was exchanged for an angiographic sheath of 6 F diameter (Radiofocus, Terumo), inserted over a stiff angiographic guidewire (Amplatz, Boston Scientific). Ultimately, 6 F brachytherapy catheters (Afterloadingkatheter, Primed Medizintechnik Gmbh) were placed in the sheaths – fixation was achieved by transient cutaneous sutures.

For further treatment planning purposes as well as for verification of correct catheter positioning, a contrast-enhanced CT in breath-holding technique or MRI scan was required and obtained. The executing interventional radiologist highlighted the target volume and lesion at risk on the newly acquired images. The HDR afterloading system (Nucletron, Elekta Ab) applied an iridium-192 source with an activity of 10 ci, installed as a single fraction irradiation.

Irradiation design and dosimetric analysis

The detailed treatment strategy was devised using the corresponding software system Oncentra (Nucletron, Elekta AB), which is an integral part of the HDR-afterloading system. After the target volume had been labeled by the interventional radiologist in every CT/MRI slice, the three-dimensional coordinates (x, y, z) of each catheter, i.e., the tip and exit at the tumor margin, were determined and transferred into the planning system. Each boundary of the target lesion was established individually for every installed catheter by specification of the distance to the reference points. The lesion/tumor enclosing reference dose, based on empiric data from prior studies, was 20 Gy installed in a single fraction and enabling a safety margin of 5 mm, i.e., the clinical target volume (Fig. 1). The specified set of reference points was used in the anatomic optimization routine of the planning software. Empiric dose limitations were taken into consideration concerning treatment of lesions in close proximity of organs at risk such as the proximal gastrointestinal system (<14 Gy/mL) (23).

During catheter removal, gelfoam or fibrin tissue glue was injected through each brachytherapy sheath to prevent post-interventional bleeding.

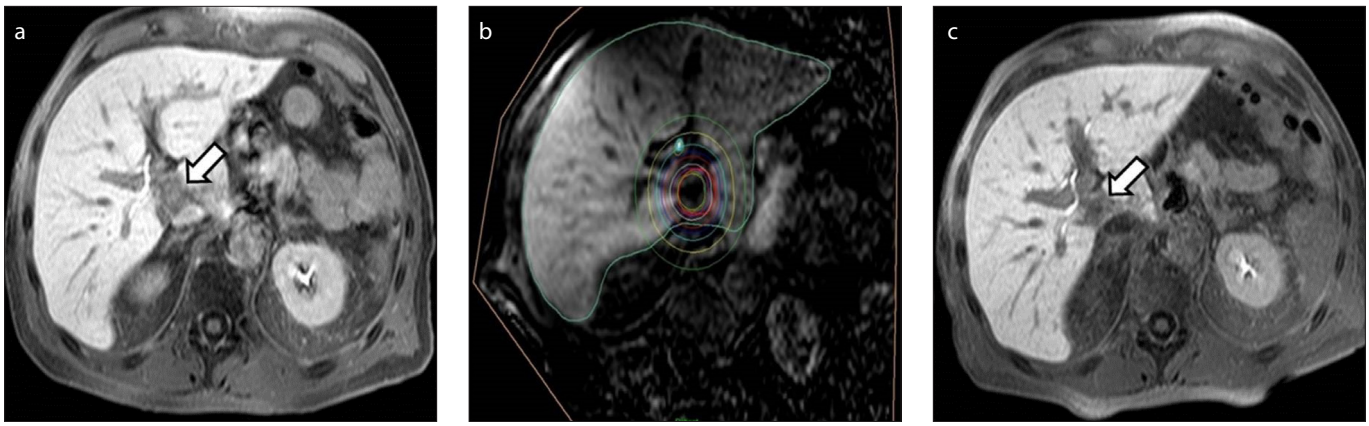

Figure 1. a–c. Local tumor control in a patient with metastatic gastric adenocarcinoma. Axial Gd-EOB-DTPA enhanced T1-weighted image **(a)** shows metastasis from gastric adenocarcinoma prior to treatment with iBT *(white arrow)*; axial Gd-EOB-DTPA enhanced T1-weighted image **(b)** shows treatment planning with marked target lesion *(red line)*, isodose lines (indicates 20 Gy) and the brachytherapy catheter *(white arrow)*; axial Gd-EOB-DTPA enhanced T1-weighted image **(c)** at 3-month follow-up shows local control of treated lesion with new Gd-EOB-DTPA enhancement defect *(white arrow)*.

Table. Patient characteristics	
Total number of patients, n	12
Patient sex, n	
Men	10
Women	2
Age at time of diagnosis (years)	
Median	63
Min–max[3]	51–71
Metastases (cumulative), n	36
Liver	29
Pancreatic	5
Lymph node	2
Type of metastatic spread	
Synchronous	4
Metachronous	8
Lesion size (cm)	
Median (Q_1–Q_3)	2 (1.4–3.6)
Min–max	1–10.2
Irradiation dose iBT (Gy)	
Median (Q_1–Q_3)	19.9 (12.9–.3)
Min–max	5.4–22.5
Irradiation time iBT (min)	
Median (Q_1–Q_3)	23.6 (16.1–.4)
Min–max	4-73
Number of catheters / lesion	
Median	2
Min–max	1–8
Local tumor control	32 (89%)
Progression-free survival (months)	
Median (Q_1–Q_3)	6.6±1.63 (3.4–10)
Min–max	1.8–46.8
95% CI	1.7–11.3

Follow-up

Whole body CT and MRI of the liver as well as clinical assessments were performed every 3 months after brachytherapy. Every patient with hepatic tumor involvement received a Gd-EOB-DTPA (Primovist) liver MRI. Changes in size and enhancement defects were correlated in a dynamic T1-weighted gradient echo sequence, diffusion-weighted imaging (DWI), post-Gd-EOB-DTPA and a T2-weighted sequence. Tumor edema was visualized in a T2-weighted sequence, vital tumor tissue in DWI and late enhancement (post-radiation) defects in the post-Gd-EOB-DTPA sequence and the dynamic sequence. Recurrence or local tumor control measurements were ultimately made in the DWI to account for vital tumor tissue and to differentiate from late enhancement defects.

Adverse events associated with the local therapy were defined according to the "Common Terminology for Adverse Events" (CTCAE) version 4.03 and the guidelines of the Society of Interventional Radiology (24). Indicators and prognostic factors of radiation induced liver disease (RILD) were the occurrence of ascites and elevated alkaline phosphatase levels or a serum bilirubin level ≥3 mg/dL in the absence of bile duct obstruction and tumor progression (25).

Definitions of remission criteria and local tumor control rates (primary endpoint)

The Response Evaluation Criteria in Solid Tumors Criteria (RECIST 1.1) categories of stable disease, partial remission, and complete remission of the treated lesions were defined as local tumor control after iBT. Progressive disease was determined as an increase in diameter >20% of any metastatic lesion.

Table. Patient characteristics (cont'd)	
Mean	9.5±3.52
Overall survival after iBT (months)	
Median	11.4±3.37(%95 CI)
Min–max (Q_1–Q_3)	4.3–47 (6.9–22.5)
95% CI	2.7–17.1
Mean	15.3±3.47(%95 CI)
Overall survival from time of diagnosis (month)	
Median	33.5
Min–max	14–86 (21.5–55.3)
Previous treatment (before iBT), n (%)	
Palliative chemotherapy	12 (100)
Resection	9 (75)
Immunotherapy	3 (25)
Selective internal radiotherapy	1
iBT image guidance	
CT	24
MRI	12
Time of hospitalization (days)	
Median	4
Min–max	3–6

Q_1–Q_3, interquartile range; 95% CI, 95% confidence interval; iBT, image guided, high-dose-rate, interstitial brachytherapy; CT, computed tomography; MRI, magnetic resonance imaging.

Statistical analysis

The primary objectives of the retrospective, single arm study were local tumor control as well as the overall safety of the iBT procedure. Overall survival and the progression-free survival were secondary objectives. Local tumor control, progression-free survival and overall survival were evaluated by employment of the Kaplan-Meier method with SPSS version 22 (SPSS, version 22.0; IBM Corp.).

Results

Between 2010 and 2016 twelve patients with histologically proven gastric adenocarcinoma, having a cumulative overall amount of 36 metastases (29 liver, 2 pancreatic, 5 lymph node) from gastric adenocarcinoma treated with iBT in our department, were included in this retrospective study (Table). At the time of referral to our institution, the metastatic gastric cancer of every patient was deemed to be in an advanced and progressive stage in the last routine follow-up staging CT. The indication for iBT, discussed in an interdisciplinary tumor board, was progressive disease, i.e., metastases showing size progression under systemic chemotherapy. The quantity of metastases upon initial referral to our institution varied from 1 to 5. The iBT procedure was in some cases applied repeatedly in separate sessions either to treat several existing lesions or newly developed metastases elsewhere.

The median patient age was 63 years (range, 51–71 years). Eleven patients had hepatic iBT treatment: 7 patients had metachronous, 4 patients had synchronous liver metastases. One patient had 2 pancreatic metastases, and another had simultaneous liver and 5 lymph node metastases, treated with iBT respectively. Prior to local ablation therapy every patient underwent palliative first-line chemotherapy with doublet or triplet regimens based on cisplatin and 5-FU. The time interval between the last chemotherapy and the iBT treatment (following the tumor board indication) was 4 weeks.

Nine patients had gastric surgery before local tumor ablation. Anti-HER-2 directed treatment was administered in 3 cases. Selective internal radiotherapy (SIRT) was performed in one case.

Five patients received additional treatment after local therapy before disease progress: three cases had another cycle of chemotherapy, one case had primary resection, and one case had immunotherapy.

The median tumor diameter was 2 cm (range, 1–10.2 cm). A median of 2 ablation catheters (range, 1–8) were used during one iBT. CT guidance was used in 24 interventions, MRI in 12. The prescribed minimal tumor dose was 20 Gy, which had to be lowered in some cases due to adjacent risk structures; a median irradiation dose of 19.9 Gy (range, 5.4–22 Gy) was applied. The total irradiation time ranged between 4 and 73 min, with a median of 23.6 min. The time of hospitalization varied between a minimum of 3 and a maximum of 6 days. One patient suffered a major complication (grade 3) and developed an infected, hepatic hematoma – successfully dealt with by transcutaneous drainage and antibiotics. Three patients received antibiotics before brachytherapy as a precaution due to cholestasis– none of them had any complication.

The localization of the 36 treated metastases from gastric adenocarcinoma was: 29 liver, 2 pancreatic, 5 lymph nodes (retroperitoneal). A cumulative number of 4 local relapses (2 hepatic, 1 lymph node, 1 pancreatic) were observed.

The specifics of the 4 local relapses, which occurred during follow-up are as follows (the given Gy values are the D99,9 tumor enclosing doses): one pancreatic metastasis with a maximum diameter of 4.5 cm was irradiated with only 5.4 Gy (2 catheters used) due to proximity of risk structures (small bowel) – the recurrence occurred 6 months later; one hepatic lesion with a maximum diameter of 5.3 cm showed no local tumor control after an irradiation dose of 16.3 Gy (7 catheters used) and a recurrence was observed after 8 months; another hepatic lesion in a different patient with a maximum diameter of 3.4 cm was irradiated with 19.69 Gy (3 catheters used) and showed a recurrence after 16 months, one lymph node with a maximum diameter of 1.6 cm in the same patient could be irradiated with only 6.46 Gy (1 catheter) and demonstrated a relapse after 12 months. In these cases, the applied dose had to be adapted due to nearby risk structures.

The range of applied doses is found in the Table. The maximum dose rises exponentially towards the irradiation center/center of the tumor but is not exactly known. However, it is much higher than the prescribed enclosing dose (D99.9) of 20 Gy.

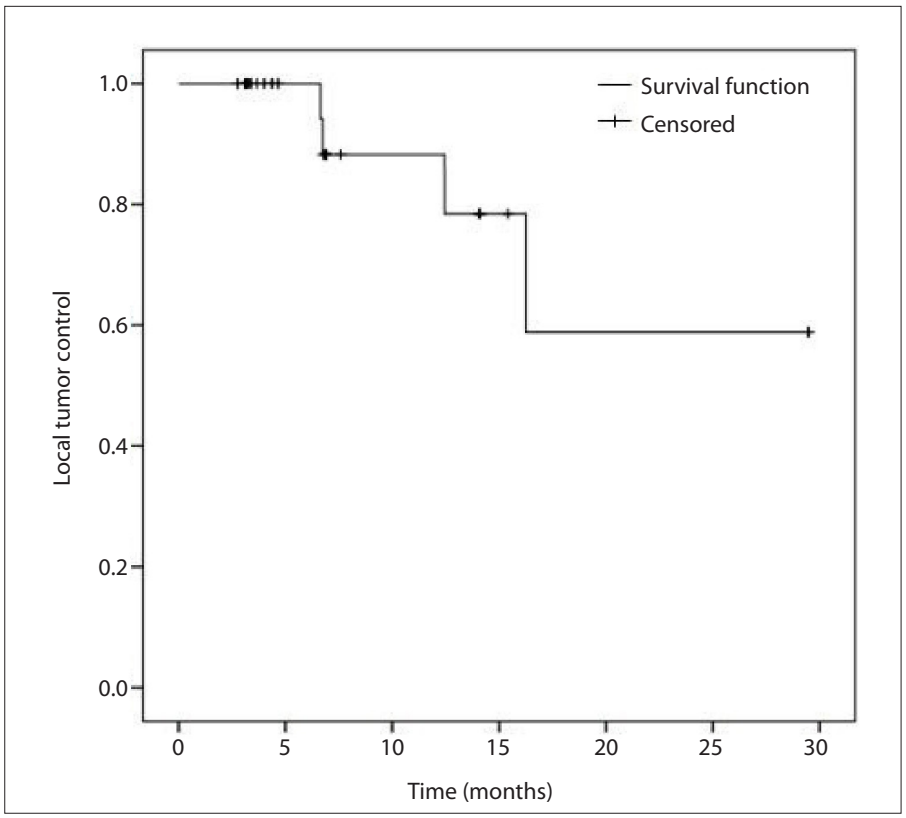

Figure 2. Local tumor control after iBT.

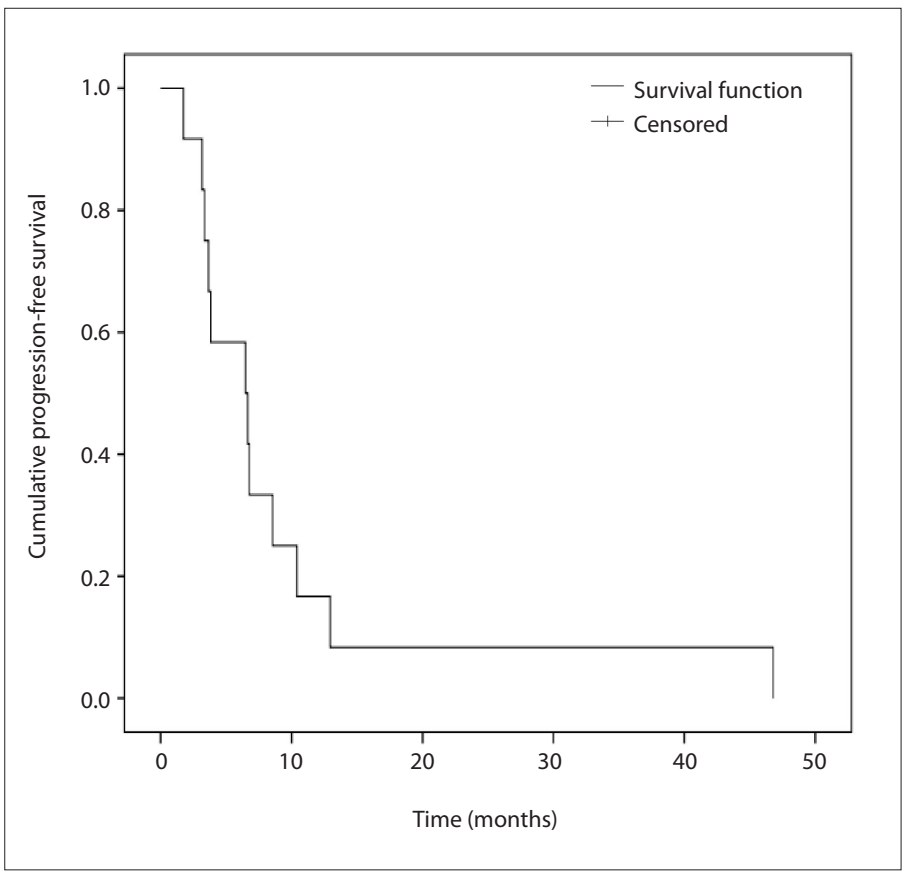

Figure 3. Progression-free survival of all patients with metastatic gastric adenocarcinoma treated with iBT.

The minimal tumor enclosing dose (clinical target volume) of 20 Gy was achieved in 23 of the 36 treated lesions (63.9%). Two doses were under 10 Gy (lymph node and pancreatic relapse); the other 11 irradiated lesions were in the range of 10.5–16.3 Gy.

Local tumor control was achieved in 89% of all lesions in the Kaplan-Meier analysis (Fig. 2). The mean follow-up time was 8.3 months. A cumulative number of 4 local relapses (2 hepatic, 1 lymph node, 1 pancreatic) were observed in 3 patients after 7 months.

The median progression-free survival was 6.5 months (Fig. 3). The median overall survival of the 12 patients with metastatic gastric cancer, calculated after iBT, was 11.4 months (Fig. 4). The overall survival from the time of diagnosis was 33.5 months.

Discussion

Surgical or local treatment of hepatic metastases from gastric adenocarcinoma is still discussed controversially (26). The liver is one of the most frequent metastasis localizations in gastric adenocarcinoma and accounts for up to 11% of metastatic lesions. No consensus about standardized or best therapeutic regimen for metastatic gastric cancer depending on disease extent has been achieved yet (27). ESMO guidelines recommend palliative chemotherapy for limited metastatic disease and reassessment for surgery depending on positive response to chemotherapy (12). Furthermore, the ESMO guidelines state that patients generally do not benefit from metastasis resection. The randomized REGATTA trial demonstrated that not even gastrectomy prolongs survival for patients suffering from limited metastatic disease (28). Therefore both gastrectomy and metastasectomy are currently considered experimental for metastatic gastric cancer patients according to the guidelines.

The 5-year overall survival rate of metastatic gastric cancer ranges from 0% to 10%. However, overall survival may be improved up to 20% after curative hepatectomy in case of liver metastases according to a meta-analysis (29). Overall survival of patients with synchronous hepatic metastases is worse than that of patients with metachronous metastases. Tumor resection or local ablation can usually only serve as a palliative treatment option and is rarely a curative approach in this setting. The rate of resection is reported as 0.5%–2.3% of all patients

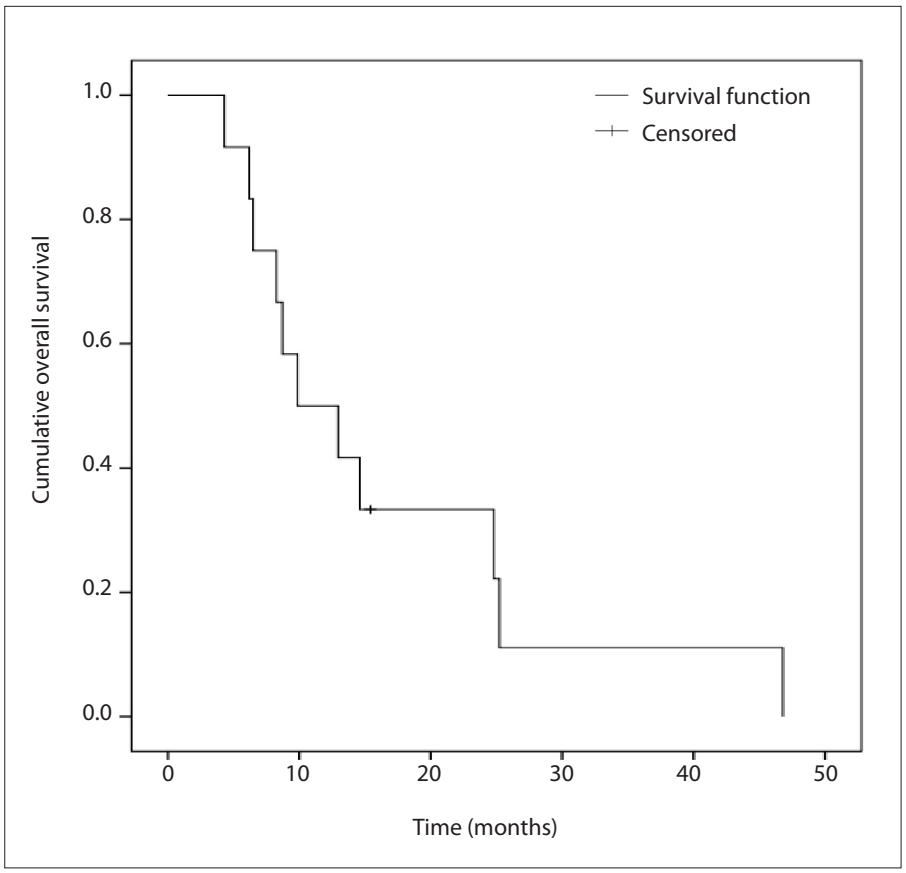

Figure 4. Overall survival of all patients with metastatic gastric adenocarcinoma ablated by iBT.

(6, 30–32). Hepatectomy is indicated in only 0.4%–1% of gastric cancer patients with liver manifestations due to multiple bilateral metastases or advanced disease with extrahepatic (peritoneal or lymphatic) dissemination (14, 33, 34). The obvious downside of surgical procedures is the higher general mortality, which is also often associated with higher patient age and several comorbidities. The few studies presently available are either not randomized, retrospective, or only include a small insignificant number of patients and in consequence the study design implies a relevant bias.

However, the FLOT 3 study, which included patients with fewer than 5 liver metastases and no other simultaneous organ manifestation, demonstrated an impressive overall survival benefit in an oligometastatic setting of 31.3 month in the surgery group versus 15.9 in the no surgery group. Patients with three or fewer liver metastases with a size <5 cm seem to benefit most of all. Limitations were the patient selection and lack of randomization. The most promising studies concerning gastric cancer seem to be the RENAISSANCE /FLOT 5 and the GASTRIPEC study, which will have to evaluate whether an aggressive surgical therapy of metastatic manifestations stemming from gastric cancer is warranted. Furthermore, several smaller retrospective studies also indicate improvement of overall survival comparing resection of gastric liver metastases with palliative chemotherapy (35).

Radiation therapy with stereotactic body radiation in metastatic gastric cancer is only described in singular case reports and does not seem to be a feasible alternative for wider application.

On the other hand, local ablation shows promising results not only in the treatment of metastatic gastric disease but also in the treatment of other tumor entities. Retrospective data suggests similar or even the same overall survival with local-ablative measures like RFA compared with surgical resection (13). Guner et al. (13) compared liver resection (n=68) and RFA (n=30) in a patient collective of 98 gastric adenocarcinoma patients and observed no significant difference in outcome; median overall survival after resection was 24 months compared with 23 months after RFA. Some smaller studies and case reports support these results and come to the same conclusion.

In contrast to RFA, brachytherapy applies an internal source of gamma radiation that results in tumor cell deactivation via DNA and RNA damage. Excellent rates of local tumor control of around 90% after 12 months are reported by several investigators treating primary and secondary liver malignancies with iBT (18, 20). There are no restrictions to tumor sites and almost every imaginable (extrahepatic) treatment site has been tested by different researchers (21, 22). Coinciding with these figures, the results of our study show a local tumor control of 89% for gastric cancer metastases, a median progression-free survival of 6.6 months and a median overall survival of 11.4 months, despite our patients being in a progressive and advance disease stage (Figs. 2–4, Table). The median overall survival calculated from the time of diagnosis was 33.5 months; at that time, four patients already had synchronous metastases. We report and confirm similar results to Geisel et al. (16) who treated esophageal and gastric cancer and stated a progression-free survival of 3.5 months after the application of iBT (16).

IBT is an overall safe procedure; only one of our patients suffered a major local complication (CTCAE grade 3), which was hepatic hematoma and abscess, successfully dealt with by transcutaneous drainage and antibiotics. Major complications (CTCAE grade 3 and 4) after iBT arise in 3% of cases according to the literature (20). In contrast, studies evaluating gastric cancer metastasis resection report up to 26.7% major complications (26).

No systemic side effects were observed and therefore time of hospitalization was short but remains a necessary safety precaution to monitor possible occult post-interventional abdominal hemorrhage. Patients usually stayed in hospital for at least two nights.

The advantages of brachytherapy over thermal ablative measures and the minimal invasive access compared with surgery are an incentive for wider application of iBT, which can be performed repeatedly in multiple sessions. Restrictions like tumor size, cooling effects /heat sink effect of large vessels do not apply to brachytherapy and therefore do not limit its efficacy. More-

over, iBT has fewer limitations concerning proximity to risk structures or other organs compared with thermal ablation procedures. Empiric observations suggest low treatment-associated morbidity and mortality compared with surgical resection due to the minimal invasive nature of the procedure, especially when iBT is performed by an experienced interventional radiologist. Patients not eligible for surgery for whatever reason should therefore be evaluated for the application of minimally invasive iBT. Another incentive to prefer iBT over extensive surgery is the preservation of liver function due to the low required security margins of 5 mm. The issue of potential needle-track metastasis was addressed specifically by irradiation of the interventional access route as a precaution.

The main indication to apply local tumor ablation in these patients was salvage therapy and, consequently, prolonged survival. Metastatic gastric adenocarcinoma has an overall survival of 11 months under palliative chemotherapy; after iBT our patients had an additional 11.4 months of overall survival (after progressing under palliative chemotherapy); thus, our goal of prolonged survival seems to have been met for the selected patient group in our study. The goal of this retrospective analysis, however, was primarily safety and applicability of the procedure and local tumor control.

The main limitation of our study, comparable to other data concerning this topic, is the low patient number due to lack of available randomized controlled trial data which could supply the needed evidence of benefit in outcome and survival to support the general and wider application of either local-ablative measures or surgical resection of gastric adenocarcinoma metastases. For the time being, any aggressive approach (surgery or local ablation) remains experimental. The current treatment rationale should be to identify appropriate candidates with limited or oligometastatic disease and whenever possible to include them in a prospective clinical study to evaluate the effectiveness of different treatment options in the anti-neoplastic toolbox. Ultimately, the aim should be prolonged survival and in very rare cases even a curative approach as well as improvement of quality of life through palliative treatment of clinical symptoms until further evidence is obtained based on prospective randomized studies.

In conclusion, the results of our study demonstrate that iBT is an overall safe procedure, and excellent local tumor control rates in the treatment of gastric cancer metastases can be achieved.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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Publikation 6

Interventionelle Verfahren bei metastasiertem kolorektalem Karzinom

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Übersicht

Einleitung

Neue Leitlinie. Die europäische Gesellschaft für medizinische Onkologie (ESMO, European Society of Medical Oncology) hat in der Augustausgabe der Annals of Oncology ihre neuen Leitlinien für das metastasierte kolorektale Karzinom (CRC) veröffentlicht [1]. Die neue Leitlinie der ESMO lässt einen Paradigmenwechsel in der Behandlung metastasierter kolorektaler Karzinome erkennen. Noch vor wenigen Jahren wäre – abgesehen von der Resektion weniger Lebermetastasen in kurativer Intention – die intensive Betonung lokal-ablativer Maßnahmen in der metastasierten Situation unmöglich gewesen. Die aktuelle Leitlinie setzt dem eine erfreuliche Akzeptanz bildgeführter interventioneller Verfahren, insbesondere in der oligometastasierten Situation, entgegen.

Bildgeführte Eingriffe. Von besonderer Bedeutung für die interventionelle Radiologie sind umfangreiche Modifikationen, die bildgeführte Eingriffe betreffen. Die 40 ESMO-Delegierten haben einen „Werkzeugkasten“ für bildgeführte ablative und lokoregionäre Therapieverfahren skizziert. Kerngedanke ist, dass die Wahl des notwendigen Werkzeuges nicht nur der individuellen Patientensituation, sondern auch der Expertise vor Ort überlassen bleiben soll. Die Wahl der Technik für eine Ablation oder eine lokoregionäre Therapie soll eine Entscheidung des multidisziplinären Teams vor Ort sein.

Verfahren. In einer entsprechenden Abbildung in der Publikation findet sich eine Liste der Verfahren, aufgeteilt nach

- Ablationen mit der Intention einer Vollremission und
- lokoregionäre Verfahren mit der Intention einer partiellen Remission.

Für die erste Gruppe sind thermische Verfahren wie Radiofrequenzablation (RFA), Kryoablation, Mikrowellenablation aufgeführt; nicht thermische Verfahren schließen die irreversible Elektroporation sowie hochkonformale hypofraktionierte Strahlentherapie wie die Stereotaxie (SBRT) und die CT-gesteuerte Brachytherapie (HDR-Brachytherapie) mit ein.

Für lokoregionäre Behandlungen nennt die Leitlinie embolische Verfahren wie die Radioembolisation und die Chemoembolisation, darüber hinaus die lokale Chemoperfusion.

Im Folgenden findet sich eine Beschreibung der onkologischen Motivation sowie der Effektivität der gängigsten ablativen und lokoregionären Verfahren aus der interventionellen Radiologie.

Es gibt einen Paradigmenwechsel in den neuen ESMO-Leitlinien: Bildgeführte interventionelle lokale Therapieverfahren des metastasierten CRC werden umfassend in die Empfehlungen aufgenommen.

Onkologische Rationale – Oligometastasierung

Bildgeführte, interventionell radiologische Verfahren haben in den letzten Jahren intensiv an Bedeutung gewonnen. Dies gilt nicht nur, aber in besonderem Maße für das metastasierte kolorektale Karzinom. Hierfür liegt eine große Zahl in der Regel retrospektiver, teilweise aber auch prospektiver Phase-II-Kohortenstudien vor, in denen einzelne oder multiple Metastasen mit lokalen oder lokoregionären Maßnahmen behandelt wurden. Allen diesen Publikationen ist gemein, dass sie für ablative Verfahren in Leber, Lunge, Nieren und Knochen wie auch für lokoregionäre Verfahren bei diffusem Leberbefall eine hohe Verträglichkeit aufweisen [2 – 7].

Überlebensvorteil. Darüber hinaus zeigen einarmige Kohortenstudien mit Einsatz der Radiofrequenzablation oder anderer thermischer Ablationsverfahren bei Lebermetastasen des kolorektalen Karzinoms ein Langzeitüberleben. Mit Blick auf die in der Regel fortgeschrittenen Krankheits- und Therapiestadien werden vorteilhafte mediane Überlebenszeiten von bis zu 53 Monaten beschrieben [2,5,8,9]. Einen Meilenstein für den Einsatz lokaler Maßnahmen beim hepatisch metastasierten kolorektalen Karzinom stellt die CLOCC-Studie dar [10, 11], die den Einsatz der Radiofrequenzablation bei Patienten mit irresektablen Lebermetastasen zusätzlich zu einer systemischen Chemotherapie untersuchte (s. „Schlüsselstudien – CLOCC“).

Schlüsselstudien

CLOCC-Studie

Die CLOCC-Studie ist eine EORTC-Studie, eine internationale Multicenterstudie, in der 152 Patienten für eine Radiofrequenzablation randomisiert wurden und bei primärer Irresektabilität eine systemische Chemotherapie erhielten. Wichtig zum Verständnis dieser Studie ist insbesondere, dass bei 47 % der für lokale Ablation randomisierten Patienten gleichzeitig eine Leberteilresektion vorgenommen wurde; diese wurde dann zum Erreichen einer R0-Resektion durch eine RFA supplementiert. Umgekehrt erhielten 12 % der Patienten im Kontrollarm eine Leberteilresektion, wenn unter der systemischen Erstlinientherapie eine Teilremission herbeigeführt und eine Resektabilität erreicht wurde. Nach einem Follow-up von im Median insgesamt 9,5 Jahren zeigte sich ein signifikanter Überlebensvorteil ($p = 0{,}01$) für die Patientengruppe, die zusätzlich zur systemischen Chemotherapie eine RFA, ggf. ergänzt durch eine Leberteilresektion, erhalten hatte. Der Unterschied im medianen Überleben betrug 46 gegen 41 Monate bei einer HR von 0,58. Das 8-Jahres-Überleben unterschied sich mit 36 gegen 9 %.

Die CLOCC-Studie zeigt einen signifikanten Überlebensvorteil für Patienten, die zusätzlich zur systemischen Chemotherapie eine Radiofrequenzablation (ggf. ergänzt durch eine Leberteilresektion) erhielten.

Offene Fragen

Die CLOCC-Studie wirft eine Reihe von Fragen auf:

Therapiekriterien. Zunächst muss man feststellen, dass die Einschlusskriterien mit bis zu 10 Lebermetastasen sehr breit gewählt worden waren, sodass sich die Frage stellt, ob man für einen Teil der Patienten eine biologisch sehr ungünstige Situation annehmen muss. Immerhin bleibt festzustellen, dass der Einsatz lokaler Maßnahmen bei leberbegrenzter Erkrankung in der Erstlinientherapie und mit der Intention einer R0-Situation einen Überlebensvorteil erwirtschaften kann. Mit Blick auf die Behandlungscharakteristika in CLOCC ist dies sicherlich unabhängig davon, ob es sich bei den lokalen Maßnahmen um bildgeführte thermische Ablationen, chirurgische Resektionen oder – in letzter Konsequenz – andere ablative Maßnahmen wie beispielsweise hochkonformale hyperfraktionierte Bestrahlung (Stereotaxie, CT-Brachytherapie) handelt.

Definition der Oligometastasierung. CLOCC wirft letztlich wie viele andere Studien auch die drängende Frage nach einer Definition der Oligometastasierung auf. Die üblichen Empfehlungen für chirurgische Eingriffe bei hepatisch metastasierten Patienten definieren eine noch kurativ angehbare Oligometastasierung nach Anzahl der Metastasen [12], wobei eine Obergrenze von 3, manchmal 5 Herden in Abhängigkeit von der Organverteilung genannt wird [1]. CLOCC hat für sich mit Einschlusskriterien bis zu 10 Lebermetastasen diese Grenzen verschoben, ohne letztlich den Nachweis zu erbringen, dass für die Patienten mit einer Vielzahl von Tumoren gleichfalls das günstige Ergebnis der Gesamtstudie gilt.

Unterschiedliche Organsysteme. Unbeantwortet ist weiterhin die Frage, ob eine Oligometastasierung auch unterschiedliche Organsysteme betreffen kann – dies wird wichtig, wenn die Effektivität lokaler bzw. lokalablativer Maßnahmen beispielsweise in der Lunge diskutiert wird. Am weitesten legen die im August 2016 in Annals of Oncology publizierten Leitlinien der ESMO die Definition der Oligometastasierung aus – ein Umstand, der für die bildgeführten lokal-ablativen Verfahren von außerordentlichem Wert ist. Basierend

auf Studien – beispielsweise von Weiser, Katthak und Price – lässt die ESMO-Leitlinie den Einsatz lokaler Verfahren bei „bis zu 2 oder gelegentlich 3 Organsystemen“ (Leber, Lunge, Lymphknoten, Ovarien) und „bis zu 5 oder manchmal mehr Läsionen“ zu, wenn mittels lokaler und lokal-ablativer Verfahren eine Tumorfreiheit („R0“) erreicht werden kann [1, 13 – 15].

Die ESMO-Leitlinie lässt den Einsatz lokaler Verfahren bei Oligometastasierung zu, wenn hierdurch eine Tumorfreiheit („R0“) erreicht werden kann.

„Werkzeugkasten“: Ablation und lokoregionäre Verfahren

Perkutane thermische Ablation

Die Radiofrequenzablation (Abb. **1**) (oder ganz allgemein: thermische Ablation) wurde in den zurückliegenden Jahren bei Irresektabilität oder auf besonderen Patientenwunsch durchgeführt. Insbesondere bei Patienten mit klar kurativer Ausrichtung wird in den üblichen Tumorkonferenzen die Resektion gegenüber der Ablation bevorzugt, selbst wenn auch die Resektion bei ungünstig lokalisierten Läsionen mit hohen R1-Raten kämpft. So publizierten Welsh et al. 2008 eine Kohorte von etwas über 1000 Patienten, bei denen bei nicht anatomischen Resektionen 24 %, bei erweitert anatomischen und nicht anatomischen 35 % R1-Resektionen resultierten. Bei Re-Resektion lag die R1-Rate bei 18 % [16]. Für die RFA sind sehr heterogene Ergebnisse bzgl. der lokalen Kontrollrate (also gewissermaßen eine R0-Situation in einem „Test-of-Time“ durch Bildgebung in der Nachsorge) zwischen 70 und 90 % nach einem Jahr publiziert. Genau wie für die chirurgische Resektion gelten auch für die RFA Einschränkungen der Effektivität in Abhängigkeit von der intrahepatischen Lokalisation oder auch Beeinflussung durch Kühleffekte großer Gefäße [17].

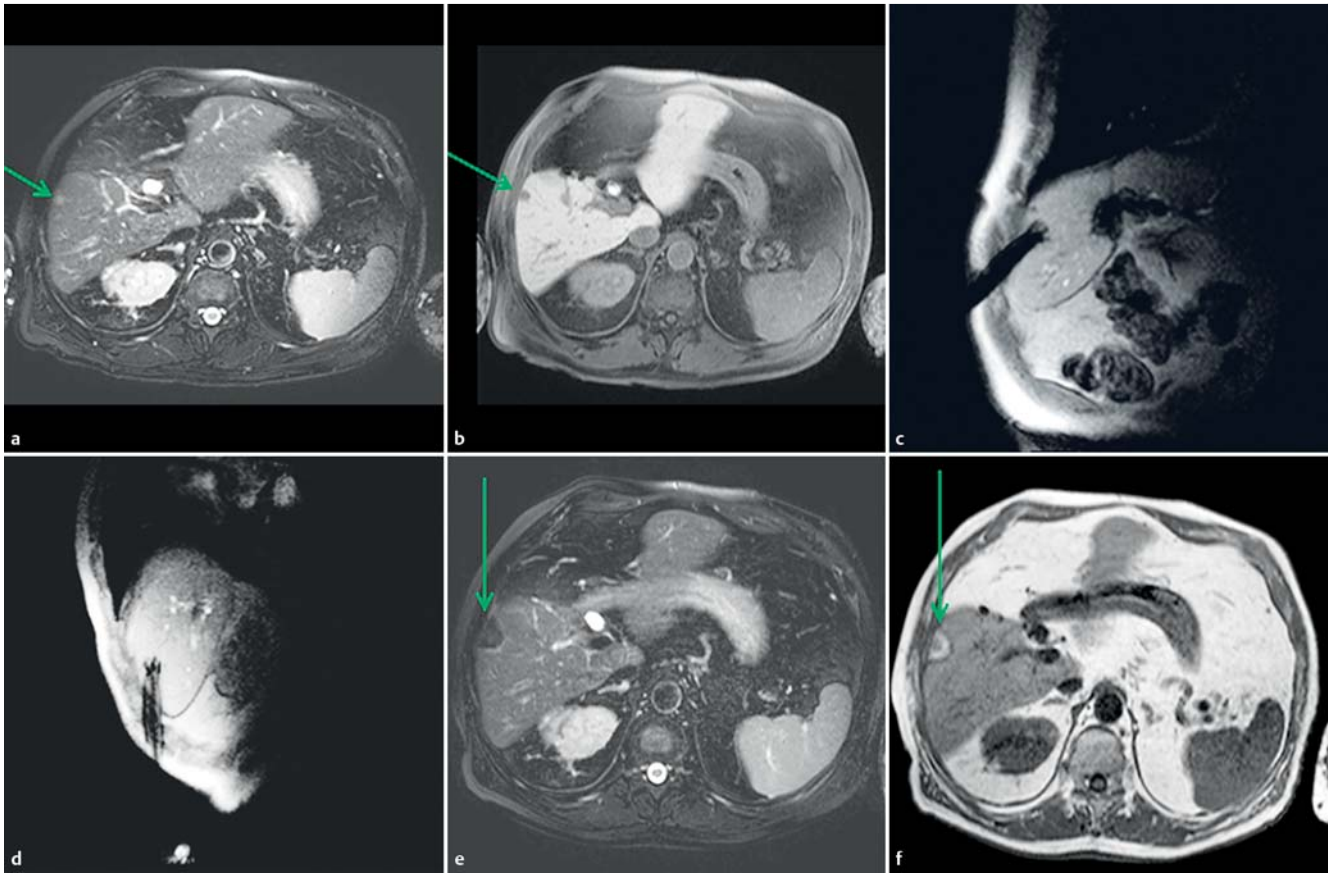

Abb. **1** Radiofrequenzablation. Patient mit Rektumkarzinom mit Lebermetastasen. Das präinterventionelle MRT zeigt eine Lebermetastase im Lebersegment VII. **a** T2 mit Fettsättigung. **b** Spätaufnahme nach Applikation von hepatozytenspezifischem Kontrastmittel. **c** und **d** Einlage der RFA-Elektrode unter MR-Bildgebung: 2-Ebenen-Bildführung angepasst an die Nadelangulation. **e** (T2 mit Fettsuppression) und **f** (T1 nativ) Postinterventionelles MRT 3 Monate nach RFA: anhaltende Remission. Pfeile kennzeichnen narbige Umbauprozesse des Ablationsareals mit diskretem perifokalen Ödem.

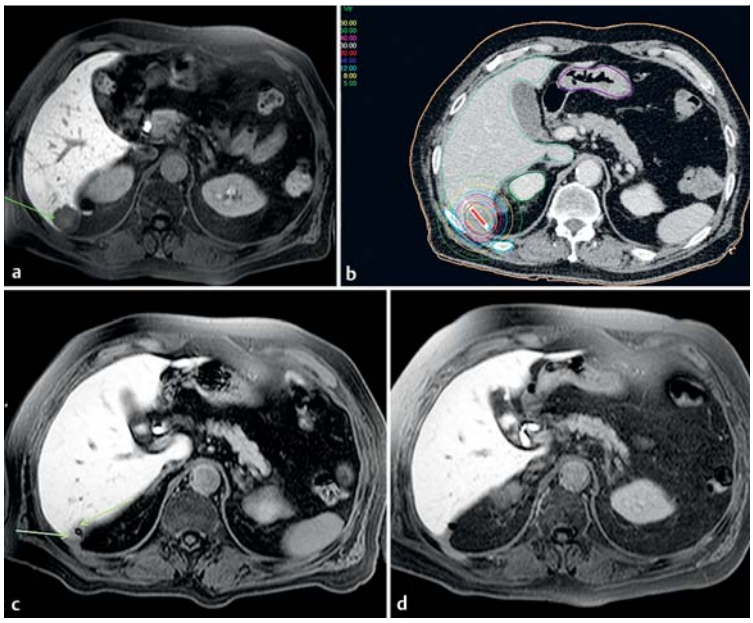

Abb. **2** Brachytherapie. **a** Patient mit hepatisch metastasiertem Sigmakarzinom. Das präinterventionelle MRT mit leberspezifischem Kontrastmittel zeigt eine Lebermetastase im Segment VI. **b** Planungs-CT mit Einlage eines Brachytherapiekatheters. Um den Katheter sind die Isodosen der Bestrahlungsplanung eingezeichnet. Es wurden tumorumschließend 20Gy (rote Linie) appliziert. **c** MRT 5 Monate nach Brachytherapie: Remission der Lebermetastase im Segment VI. Strahleninduzierter Funktionsausfall des umgebenden Leberparenchyms, Pfeile kennzeichnen ein Speicherdefizit in der Spätphase nach Applikation von hepatozytenspezifischem Kontrastmittel. **d** MRT 2 Jahre nach Brachytherapie: Anhaltende Remission. Regeneriertes Leberparenchym ohne nachweisbaren Funktionsausfall (regelrechte Speicherung des hepatozytenspezifischen Kontrastmittels).

RFA vs. chirurgische Resektion. Einen interessanten Einblick in die Möglichkeiten der lokalen Kontrolle nach RFA oder chirurgischer Resektion erlaubt eine Publikation von Tanis et al. aus dem Jahre 2013 [18]. Diese Gruppe hat die Rohdaten der EPOC-Studie und der CLOCC-Studie miteinander verglichen. Herangezogen wurden Patienten aus der EPOC-Studie mit hepatischer Resektion und aus der CLOCC-Studie mit RFA bei gleicher systemischer Chemotherapie, sodass die beiden Datensätze aus diesen zwei unterschiedlichen Studien sehr gut miteinander vergleichbar sind. Über alle Läsionen betrachtet, lag die Rate der R0-Resektionen bzw. die lokalrezidivfreie Rate für die Chirurgie bei 93,5 % und für die RFA bei 94 %. Interessanterweise lag die R1-Rate bei Läsionen über 3 cm für chirurgische Resektion bei 0 %, wohingegen bei Läsionen unter 3 cm eine R1-Resektionsrate von 6,1 % vermerkt wurde. Für die RFA verhielt es sich genau umgekehrt: Bei Läsionen über 3 cm lag die Lokalrezidivrate bei 21,4 %, bei Läsionen unter 3 cm bei 2,9 %. Die Erklärung hierfür dürfte sein, dass die Patienten in der EPOC-Studie mit großen Tumoren eine ausgedehntere Leberteilresektion, wie beispielsweise eine Hemihepatektomie, mit naturgemäß großem Sicherheitssaum durchliefen, wohingegen bei kleinen Herden gehäuft atypische Resektionen durchgeführt wurden. Die RFA verliert mit einem Schwellwert von etwa 3 cm erheblich an Effektivität und das Risiko des Verlustes der lokalen Kontrolle steigt deutlich an.

Eine mögliche Schlussfolgerung ist, dass insbesondere dann in einer potenziell kurativen Situation die chirurgische Resektion der RFA vorzuziehen ist, wenn segmental bzw. anatomisch reseziert werden und ein komfortabler Sicherheitssaum eingehalten werden kann; Läsionen oberhalb von 3 cm sollten möglichst nicht mittels thermischer Ablation behandelt werden.

Bei Läsionen unter 3 cm ist die R1-Rate der RFA kleiner als bei chirurgischer Resektion. Bei Läsionen über 3 cm verliert die RFA an Effektivität und eine chirurgische Resektion ist ihr vorzuziehen.

Hochkonformale hypofraktionierte Bestrahlung: CT-gesteuerte Brachytherapie

Die CT-gesteuerte Brachytherapie (Abb. **2**) zählt zu den hochkonformalen hypofraktionierten strahlentherapeutischen Verfahren, die von der ESMO in die Leitlinien zur Behandlung des metastasierten kolorektalen Karzinoms aufgenommen worden sind [1]. Die CT-gesteuerte Brachytherapie ist ein Verfahren, das üblicherweise interdisziplinär von Strahlentherapie und interventioneller Radiologie durchgeführt wird. Der arbeitsteilige Auftrag der interventionellen Radiologie ist hierbei die bildgeführte, üblicherweise unter CT-Fluoroskopie vorgenommene Positionierung der die Strahlenquelle aufnehmenden Katheter in Tumormanifestationen innerer Organe. Die eigentliche Bestrahlung mit einer Iridium-192-Quelle erfolgt dann in der Strahlentherapie.

Vorteile gegenüber Stereotaxie. Herausragender Vorteil der CT-gesteuerten Brachytherapie gegenüber der gleichfalls in den ESMO-Leitlinien genannten Stereotaxie ist der flexiblere Einsatz insbesondere bei sehr großen Tumoren oder bei einer Vielzahl von Tumoren in Leber oder Lunge. Für die Größenkriterien gilt, dass in einer Studie an 73 Patienten mit 199 Lebermetastasen von im Median 5 cm Größe (1 – 13 cm) eine lokale Kontrollrate von 90 % nach 12 Monaten erzielt wurde, wenn eine tumorumschließende Dosis von 20 Gy erreicht wurde [3]. Das mediane Überleben betrug ab Brachytherapie 23,4 Monate und ab Erstdiagnose der Lebermetastasen 46,4 Monate, was wiederum die erhebliche

Vortherapie der behandelten Patienten unterstreicht. Die Ergebnisse scheinen reproduzierbar, wie publizierte Daten von Colletini et al. zeigen: Behandlung von 80 Patienten mit 179 Lebermetastasen, im Mittel 2,8 cm Größe (0,8 – 10,7 cm), medianes Gesamtüberleben ab Brachytherapie 18 Monate [19].

Erwähnt werden sollte, dass die tumorumschließende, also 100 % des Zielvolumens abdeckende Dosis von 20 Gy nur die geringste Dosis am Tumor anzeigt. Aufgrund der Bestrahlung von innen nach außen (also aus dem Katheter heraus) wird im Gegensatz zur Stereotaxie eine außergewöhnliche Heterogenität erzielt, d. h. die Dosen im Zielvolumen und insbesondere zwischen den Kathetern sind üblicherweise exorbitant und erhöhen somit die biologische Wirksamkeit gegenüber der Stereotaxie, die als dosishomogenes Verfahren mit Einzeldosen von ca. 20 Gy üblicherweise in etwa 3 oder auch 5 Fraktionen durchgeführt wird. Die CT-gesteuerte Brachytherapie ist demgegenüber in aller Regel eine Einzeittherapie, bei der die Iridiumquelle etwa 40 – 60 min in den Kathetern verbleibt, die ihrerseits unmittelbar nach dem Eingriff unter Verschluss der Punktionskanäle gezogen werden [20].

Die CT-gesteuerte Brachytherapie zählt zu den in den ESMO-Leitlinien aufgenommenen lokalen Therapieverfahren des metastasierten CRC. Das Verfahren sieht in der Regel, anders als die Stereotaxie, ein einzeitiges Vorgehen vor.

Ein weiterer Vorteil der Bestrahlung von innen nach außen ist die bessere Dosisverteilung bzgl. umgebender Risikoorgane. In der Praxis werden im Rahmen der Stereotaxie maximal 3 Leber- oder Lungenmetastasen bestrahlt, da durch die konformale Bestrahlung durch Einstrahlen von außen ein zwar gering dosiertes Dosisbad für Leber oder Lunge entsteht, das aber bei mehrfachem Einsatz zu einer kumulativen Dosis führen kann, die wiederum die Toleranz gesunden Leber- oder Lungenparenchyms übersteigt.

Individuelle Therapieentscheidung. In der Zusammenschau handelt es sich bei ähnlichen Ergebnissen für die zu erzielende lokale Kontrolle von Läsionen um individuelle Entscheidungen für Stereotaxie oder Brachytherapie, die insbesondere bei solitären Läsionen die höhere Invasivität der CT-Brachytherapie mit Katheteranlage berücksichtigen.

Vorteile gegenüber RFA. Gegenüber der RFA bzw. thermischen Ablation von Vorteil sind neben dem technisch kaum vorhandenen Größenlimit die Möglichkeit ubiquitären Einsatzes sowohl in Leber und Lunge als auch außerhalb sowie die Unempfindlichkeit gegenüber Kühleffekten [20 – 22]. Günstige lokale Kontrollraten wurden auch für Lungenherde publiziert, die in aller Regel bei Behandlung deutlich kleiner (bis 2 cm) waren. Die lokale Kontrollrate nach 12 Monaten für gemischte Tumorbiologie lag bei 90 % [23, 24].

Vorteile einer CT-gesteuerten Brachytherapie gegenüber der RFA sind: kaum Effektivitätsverluste durch Größe der Metastasen noch durch umgebende Kühleffekte durch Gefäße. Mit der CT-gesteuerten Brachytherapie sind zudem auch zentrale Metastasen (Nähe zur Gallengangsgabel) gut behandelbar.

Lokoregionäre Verfahren

Yttrium-90-Radioembolisation

^{90}Y-Radioembolisation (synonym SIRT: selektive interne Radiotherapie) ist ein interventionelles Verfahren, bei dem ein an Mikrosphären gekoppelter Betastrahler zur Behandlung primärer oder sekundärer Lebermalignome selektiv über die Leberarterie appliziert wird.

Additive ^{90Y}-Radioembolisation. Die SIRFLOX-Studie untersuchte den Effekt einer zusätzlichen ^{90}Y-Radioembolisation bei Patienten mit nicht resektablen Lebermetastasen eines CRC, die als Chemotherapie mFOLFOX6 erhielten (s. „Schlüsselstudien – SIRFLOX-Studie“).

Ein Blick auf die Patientencharakteristika von SIRFLOX mit 46 gegen 45 % Primärtumor in situ und in jeweils 40 % Vorliegen einer extrahepatischen Metastasierung (jeweils experimenteller Arm gegen Kontrolle) verdeutlicht, warum die Wahl des Endpunktes „progressionsfreies Überleben“ (im gesamten Körper) für die SIRFLOX-Studie ein enormes Risiko darstellte und schließlich auch zum Verfehlen des *primären* Endpunktes führte: Die ^{90}Y-Radioembolisation ist ein lokoregionäres Verfahren, das allein auf die Lebermetastasierung angewendet wird, die extrahepatische Metastasierung bleibt unbehandelt. Schaut man also auf die sekundären Endpunkte, so findet man bemerkenswerterweise ein ganz erhebliches Signal für die Kontrolle fortgeschrittener metastasierter kolorektaler Karzinome unter Bezug auf die Lebermetastasierung: Das progressionsfreie Überleben (PFS) in der Leber, also das Organ bzw. die Metastasen, die tatsächlich von der ^{90}Y-Radioembolisation direkt erreicht werden, wurde durch

Schlüsselstudien

SIRFLOX-Studie

SIRFLOX ist eine prospektive Multicenterstudie, die als Phase-III-Studie konzipiert den additiven Wert der ^{90}Y-Radioembolisation mit Kunstharz-Mikrosphären (Sirspheres) bei nicht resektablen Lebermetastasen des kolorektalen Karzinoms untersucht hat [7]. Eingeschlossen wurden 530 chemonaive Patienten, die mit mFOLFOX6 (optional kombiniert mit Bevacizumab) behandelt und nach ^{90}Y-Radioembolisation oder keine ^{90}Y-Radioembolisation randomisiert wurden. Primärer Endpunkt war das progressionsfreie Überleben (unabhängige Begutachtung nach RECIST 1.0); sekundäre Endpunkte waren u. a. progressionsfreies Überleben in der Leber und Gesamtüberleben. Eingeschlossen wurden u. a. Patienten mit extrahepatischer Metastasierung (bis zu < 5 Lungenmetastasen ≤ 1 cm oder singuläre Lungenmetastase ≤ 1,7 cm oder Lymphknotenmetastasen < 2 cm in einer anatomischen Region). Die Randomisation von 267 gegen 263 Patienten (mit/ohne ^{90}Y) erfolgte 1 : 1. Jeweils etwa 66 % der Patienten zeigten ECOG 0 und 34 % ECOG 1. Bei 46 und 45 % der Patienten war der Primärtumor in situ belassen; jeweils 40 % der Patienten wiesen extrahepatische Metastasen auf; 27 und 30 % eine hepatische Tumorlast > 25 %. Der Anteil synchroner Metastasierung lag bei 89 und 90 %.

Die Anzahl der Patienten mit ≥ Grad-3-Toxizität erreichte 198 und 210 (^{90}Y/Kontrolle). Signifikante Unterschiede in der Anzahl der Chemotherapiezyklen, -dauer und -dosierung zeigten sich nicht. Der Unterschied zwischen den Ereignissen Neutropenie (40,7 vs. 28,5 %), febrile Neutropenie (6,1 vs. 1,9 %), Thrombozytopenie (9,8 vs. 2,6 %) und Fatigue (10,6 vs 4,8 %) war signifikant zwischen ^{90}Y und Kontrolle. Radioembolisationsassoziierte Ereignisse waren Magen- oder Duodenalulzera bei 3,7 %, Aszites, Leberversagen und Strahlenhepatitis bei 2,8, 1,2 und 0,8 % [7].

Der primäre Endpunkt progressionsfreies Überleben wurde verfehlt mit einem Median von 10,7 gegen 10,2 Monate (HR 0,93; 95 % CI 0,77 – 1,22, p = 0,43). Für den sekundären Endpunkt Leberprogression ergab sich ein medianer Vorteil von 20,5 vs. 12,6 Monaten (^{90}Y/Kontrolle, p = 0,002). Die Überlebensdaten werden mit zwei weiteren, weitgehend identischen Studien (FOXFIRE, FOXFIRE global) gepoolt und für 2017 erwartet.

Zusatz der ^{90}Y-Radioembolisation gegenüber der Kontrolle um 8 Monate verbessert.

SIRFLOX-Studie: ^{90}Y-Radioembolisation plus First-Line-Therapie mit FOLFOX (± Bevacizumab) verbessert das PFS in der Leber um 8 Monate gegenüber der alleinigen First-Line-Therapie. Das gesamte PFS zeigte jedoch keinen signifikanten Unterschied. Daten zum Gesamtüberleben stehen aus.

Gesamtüberleben. Die Frage nach der Relevanz der Ergebnisse der SIRFLOX-Studie für das Gesamtüberleben der Patienten bleibt aktuell noch unklar. Die ESMO hat sich dementsprechend in ihrer letzten Leitlinie in Kenntnis der SIRFLOX-Ergebnisse darauf festgelegt, den Einsatz der ^{90}Y-Radioembolisation lediglich in der Salvage-Situation für leberdominante Patienten zu empfehlen [1]. Diese Empfehlung stützt sich neben den SIRFLOX-Daten auf multiple Phase-II-Kohortenstudien, eine randomisierte Studie sowie eine Matched-Pair-Studie, die einen günstigen Einfluss der ^{90}Y-Radioembolisation bei leberdominanter Erkrankung annehmen lassen. Bester et al. haben in einer 224 Patienten mit kolorektalen Karzinomen einschließenden Kohortenstudie einen Vergleich mit 29 weiteren Patienten publiziert, die als Teilnehmer derselben Studienkohorte aus prognostisch nicht relevanten Gründen, wie dem Vorliegen anatomischer Varianten in der leberarteriellen Versorgung, dem Rückzug der Konsentierung für eine Radioembolisation o. Ä., die Radioembolisation nicht erhalten und stattdessen eine Best Supportive Care durchlaufen haben. Der Überlebensvorteil für die Embolisationskohorte war hochsignifikant (11,9 gegen 6,6 Monate medianes Gesamtüberleben) [25]. Gleichfalls signifikant war der Überlebensvorteil einer Gruppe von Patienten, die in einer Matched-Pair-Analyse von Seidensticker et al. eine ^{90}Y-Radioembolisation erhalten hatten im Vergleich zu Patienten mit Best Supportive Care oder auch ergänzenden chemotherapeutischen Maßnahmen, wie einer Kombination aus Mitomycin und Xeloda (8,3 gegen 5,5 Monate medianes Gesamtüberleben). Diese 58 Patienten waren gematched nach den Kriterien Tumorlast (± 20 %), Auftreten der Lebermetastasierung (synchron vs. metachron), Erhöhung der alkalischen Phosphatase über den oberen Grenzwert und Erhöhung des CEA (≥ 200 ng/ml vs. < 200 ng/ml) [26]. Trotz der kleinen Patientenzahl (44 Patienten) von besonderem Stellenwert ist eine randomisierte Studie von Hendlisz et al. aus dem Jahre 2010, bei der Patienten mit einer Salvage-Therapie bei Refraktärität mit 5-FU i. v. zu ^{90}Y-Radioembolisation oder keine ^{90}Y-Radioembolisation randomisiert wurden. Die Patienten mit ^{90}Y-Radioembolisation zeigten ein signifikant verlängertes PFS (5,5 vs. 2,1 Monate), wobei der Effekt auf das Gesamtüberleben nicht signifikant war (10,0 vs. 7,3 Monate), was aber gut durch ein erlaubtes Cross-over in den Therapiearm bei Progress erklärbar ist [27].

Der positive Effekt einer ^{90}Y-Radioembolisation auf das Gesamtüberleben in der therapierefraktären Situation konnte durch mehrere Studien aufgezeigt werden.

Prognostische Faktoren: TuCK-Score. Besonders hervorzuheben ist eine jüngst erschienene Phase-II-Kohortenstudie von Damm et al., die sich gezielt um die Identifikation von Patienten bemüht, die in einer fortgeschrittenen therapierefraktären bzw. Salvage-Situation von einer ^{90}Y-Radioembolisation profitieren [28]. Es handelt sich um eine Kohorte von 116 Patienten in der therapierefraktären Situation, die eine leberdominante Metastasierung eines kolorektalen Karzinoms aufwiesen. Lungenmetastasen fanden sich bei 10 %, Knochenmetastasen 3 %, Lymphknotenmetastasen bei 25 % der Patienten. Alle Patienten durchliefen eine ^{90}Y-Radioembolisation. Das Überleben der Patienten wurde hinsichtlich prognostischer Faktoren analysiert. In der multivariaten Analyse wurden eine Tumorlast von mehr als 20 %, ein CEA > 130 ng/ml und/oder CA19 – 9 > 200 ng/ml sowie ein Karnofsky-Index < 80 als prognostisch relevant identifiziert. Außerordentlich interessant sind die ermittelten Überlebenskurven in Abhängigkeit von der einzelnen oder kumulativen Anwesenheit der genannten Faktoren. Verleiht man jedem dieser einzelnen Faktoren einen Punkt (Tumorlast, CEA oder CA19 – 9, Karnofsky = TuCK-Score), so ergeben sich für Punktwerte von 0, 1, 2 und 3 signifikante und höchst eindrucksvolle Unterschiede im Überleben. Insbesondere die Trennung der Patientengruppe in Patienten mit 0 und 1 gegenüber 2 und 3 Punkten ist für eine klinische Bewertung der Sinnhaftigkeit einer ^{90}Y-Radioembolisation in der therapierefraktären Salvage-Situation äußerst wertvoll: Für einen TuCK-Score 0 und 1 ergibt sich ein medianes Überleben von 10,4 Monaten, für einen Score von 2 und 3 von nur 5,1 Monaten ($p < 0,05$) [28]. Insbesondere die Überlebenskurve bei einem TuCK-Score von 3 dürfte sich kaum vom natürlichen Krankheitsverlauf der betroffenen Patienten unterscheiden, sodass die Durchführung einer letztendlich doch sehr eingreifenden Therapie wie der ^{90}Y-Radioembolisation bei solchen Patienten kaum empfohlen werden kann.

Zu ähnlichem Ergebnis kommt die Arbeitsgruppe von Jakobs et al. in einer Publikation aus diesem Jahr. In einem Patientenkollektiv, das auf schwerstkranke Patienten wie bei Damm et al. verzichtet und in etwa einem TuCK-Score von 0 – 1 entsprechen dürfte, erzielen Jakobs et al. ein medianes Überleben in der therapierefraktären Situation von 10,2 Monaten [6].

Der TuCK-Score umfasst die prognostischen Faktoren Tumorlast, CEA oder CA19 – 9 und Karnofsky-Index, welche das individuelle Ergebnis nach einer ^{90}Y-Radioembolisation hinsichtlich des medianen Überlebens stark beeinflussen.

Chemoembolisation mit Irinotecan-eluting Beads

Ein weiteres lokoregionäres Verfahren zur Therapie von inoperablen Lebermetastasen eines kolorektalen Karzinoms stellt die transarterielle Chemoembolisation (TACE) dar. Die TACE basiert auf einer Zellzerstörung durch einen synergistischen Effekt der arteriellen Okklusion und der lokalen Zytostatikatherapie, wobei die durch die Embolisation hervorgerufenen hypoxischen Bedingungen die Aufnahme des Chemotherapeutikums im Tumor verstärken. Etabliert ist das Verfahren in der Behandlung des hepatozellulären Karzinoms (HCC) im Bridging für eine Lebertransplantation und in der palliativen Behandlung von Patienten im intermediären Stadium (nach BCLC [Barcelona Clinic Liver Cancer]) [29]. In der Therapie von kolorektalen Lebermetastasen kommen in der Regel Kunststoffsphären zum Einsatz, die mit Irinotecan beladen sind (Drug-eluting Beads, DEBIRI).

Wirksamkeit. In den letzten Jahren evaluierten einzelne Studien die Effizienz sowie die Verträglichkeit einer DEBIRI-TACE, wobei die Evidenz dennoch nach wie vor gering ist. So zeigten Fiorentini et al. in einer randomisierten Studie mit 74 Patienten mit Lebermetastasen eines kolorektalen Karzinoms, von denen ca. zwei Drittel bereits mindestens eine Second-Line-Chemotherapie durchlaufen hatten, einen statistisch signifikanten Vorteil einer DEBIRI-Behandlung gegenüber einer systemischen Therapie mittels FOLFIRI bzgl. des Gesamtüberlebens (22 vs. 15 Monate) und des PFS (7 vs. 4 Monate) bei besserer Lebensqualität [30].

Im Mai 2016 publizierten Bhutiani et al. eine Studie zur Beurteilung der Wirksamkeit und Verträglichkeit der DEBIRI-Therapie bei therapierefraktären Patienten. In dieser einarmigen Studie zeigte sich eine Überlebensrate von 77 % nach 12 Monaten [31].

In einer Studie von Fiorentini et al. wurde ein statistisch signifikanter Vorteil einer DEBIRI-TACE-Behandlung gegenüber einer systemischen Therapie mittels FOLFIRI bzgl. des Gesamtüberlebens und des PFS beschrieben.

Offene Fragen. Trotz dieser für die DEBIRI-Therapie sprechenden Ergebnisse sollte ein wesentlicher Aspekt nicht außer Acht gelassen werden: Bei Irinotecan handelt es sich um ein Prodrug, das in gesunden Leberzellen in den aktiven Metaboliten SN-38 überführt wird. Erst der Metabolit SN-38 führt mit seiner 1000-fach höheren Wirksamkeit als Irinotecan zur gewünschten Hemmung der Topoisomerase und damit zur zystostatischen Wirkung. Dieser Wirkungsmechanismus lässt einige Fragen bei der intraarteriellen Anwendung von Irinotecan offen: In welches Gewebe ist das Irinotecan zu injizieren? Soll es so selektiv wie möglich in den Tumor appliziert werden (wie bei der TACE des HCC), obwohl eine Metabolisierung in die aktive Form nur in Leberzellen stattfindet? Oder ist gerade die unselektive Applikation mit partieller Parenchymembolisation erwünscht, um die erforderliche Umwandlung von Irinotecan in SN-38 zu erreichen? Letztere Variante birgt zwangsläufig das Risiko einer gesteigerten Lebertoxizität. Zudem ist die Rationale einer lokalen Applikation des Irinotecans bei chemorefraktären Patienten, also Patienten, die kein Ansprechen unter systemischer Applikation des Irinotecans zeigten, schwer vermittelbar. Diese Fragen sind laut aktueller Studienlage nicht ausreichend geklärt und sollten Anlass für weitere Studien geben, womit die Anwendung zunächst auf den Studienrahmen beschränkt bleiben sollte.

Die aktuelle Datenlage indiziert, dass DEBIRI-TACE in palliativer Intention einen positiven Effekt auf das Gesamtüberleben hat, wobei die Anwendung zunächst auf den Studienrahmen beschränkt bleiben sollte.

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Kernaussagen

Stellenwert

- Lokale und lokoregionäre Verfahren zur additiven Therapie des metastasierten kolorektalen Karzinoms konnten sich in den letzten Dekaden zunehmend durch überzeugende Daten etablieren und finden vermehrt Akzeptanz in den einschlägigen Guidelines, so auch in den kürzlich neu aufgelegten ESMO-Guidelines. Dies gilt insbesondere für die oligometastasierte Situation.
- Die Wahl des ablativen Verfahrens obliegt laut ESMO-Guidelines dem multidiziplinären Team vor Ort.

Verfahren

- Als Verfahren mit einer Chance auf eine R0-Ablation gelten neben der Resektion insbesondere die thermobasierten Verfahren. Gerade bei Tumoren unter 3 cm scheint hier kein Nachteil gegenüber der Resektion zu bestehen.
- Das lokal-ablative Therapiespektrum wird durch die CT-gesteuerte Hochdosis-Brachytherapie und die stereotaktische Bestrahlung komplettiert, wobei diese Verfahren insbesondere bei ungünstigen Bedingungen für thermobasierte Verfahren (nicht resektable Tumoren > 3 cm und Nähe zu hitzesensiblen Strukturen) zu erwägen sind.
- Als additiv lokoregionäres Therapieverfahren weist die ^{90}Y-Radioembolisation die solideste Datenlage auf mit resultierender Empfehlung in den ESMO-Guidelines in der Salvage-Situation. Bezüglich der Anwendungsempfehlung der ^{90}Y-Radioembolisation in früheren Stadien (primär First-Line-Therapie) sind Überlebensdaten großer prospektiv randomisierter Studien abzuwarten.

Magdeburg tätig. Der Schwerpunkt seiner klinischen und wissenschaftlichen Tätigkeit liegt in der minimalinvasiven Onkologie. Er ist wissenschaftlicher Leiter der Deutschen Akademie für Mikrotherapie.

Jens Ricke

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Publikation 7

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).

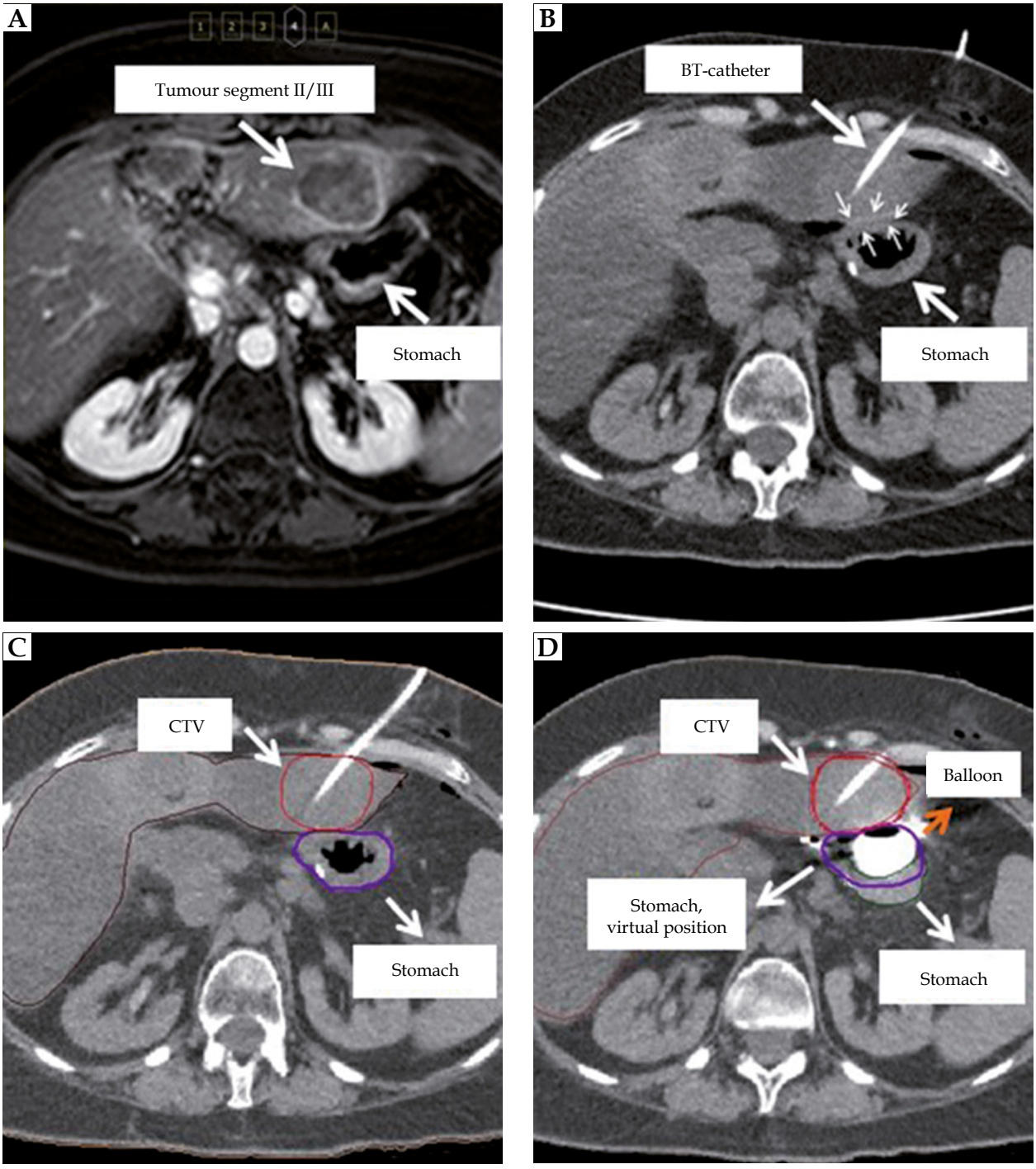
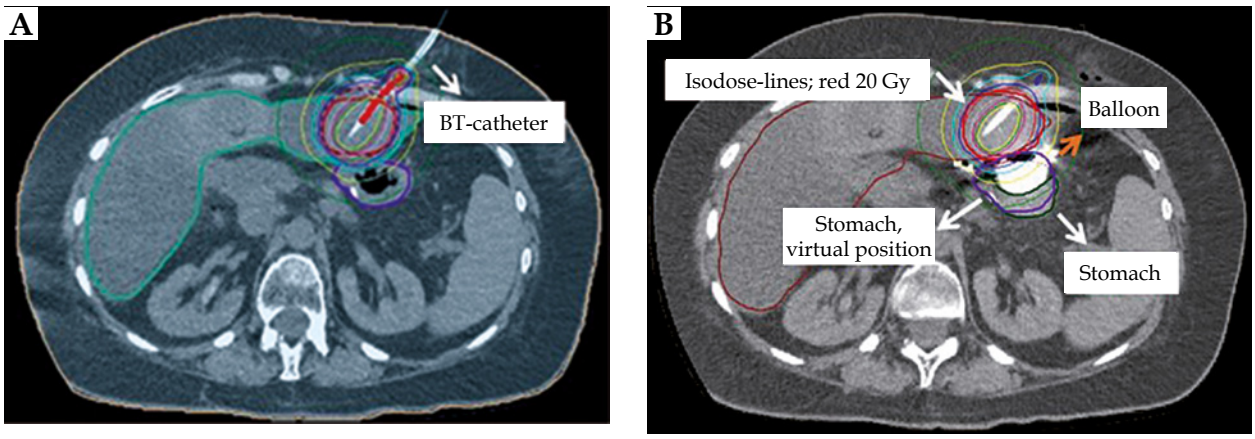


Fig. 1. Tomography imaging: **A**) Transversal MRI-scan: tumor lesion with marginal enhancement of contrast media, no BT, catheter; distinctly adjacent stomach; **B**) Corresponding transversal CT-scan with stomach position without balloon; one BT, catheter inserted; **C**) Corresponding transversal 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-

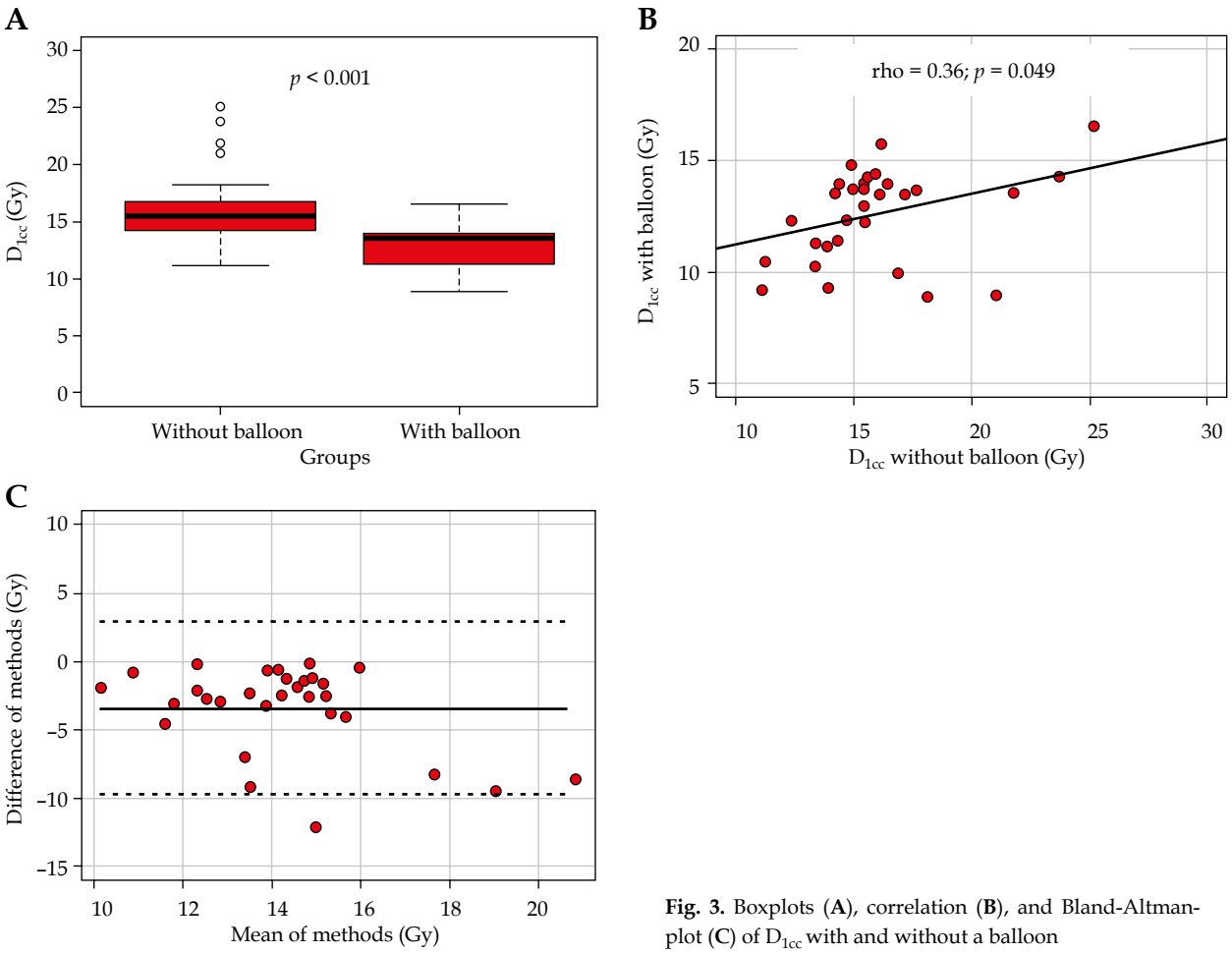


Fig. 3. Boxplots (**A**), correlation (**B**), and Bland-Altman-plot (**C**) of D_{1cc} with and without a balloon

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.

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Publikation 8

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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Key words

brachytherapy, interventional procedures, ultrasound computed tomography (US/CT)

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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.

Citation Format

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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 sonografisch erfolgreich ohne Zuhilfenahme der CT-Fluoroskopie vor-

genommen 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 as often as technically feasable (see ► **Fig. 1**). The free-hand punc-

ture 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.

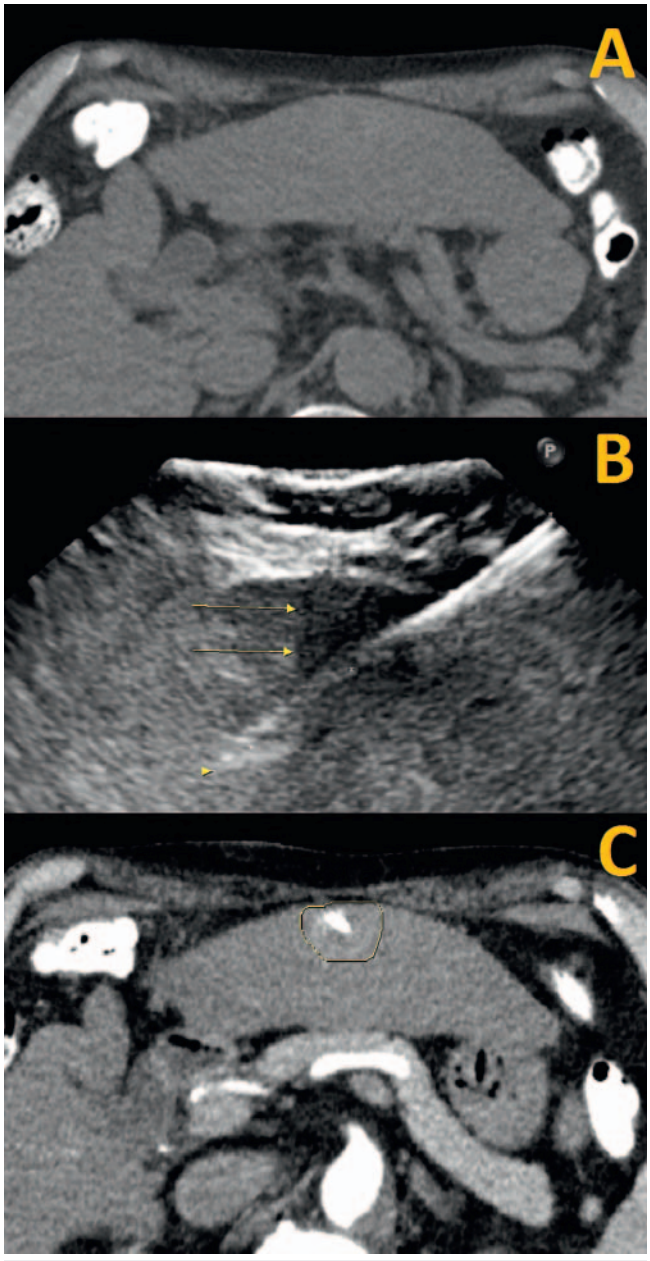
Fluoroscopy Time and Lesion Visibility

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.

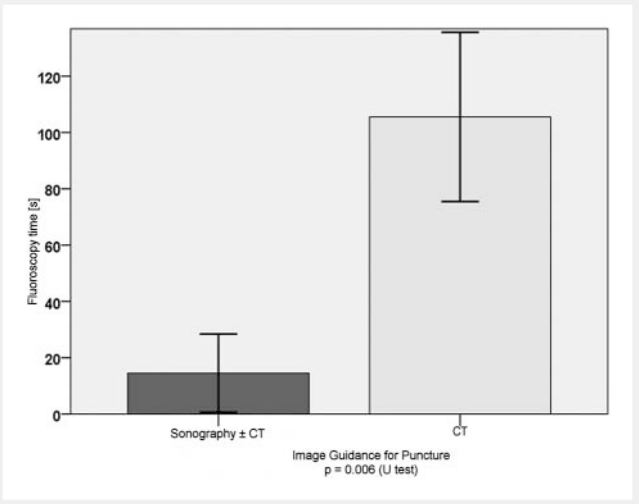
Interstitial Tumor Ablation

The tumor-enclosing dose during single fraction irradiation was set at 15 to 25 Gy, depending on the tumor entity, and the mean 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 pa-

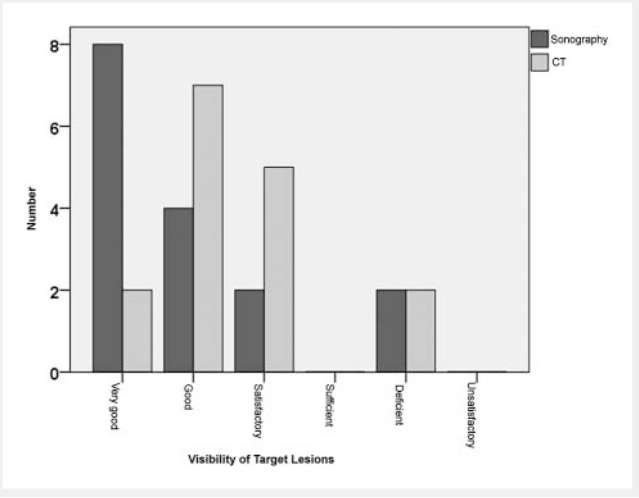


▶ **Fig. 2** Interstitial brachytherapy of a subcapsular HCC in liver segment III. The lesion is barely visible in non-enhanced CT **A** although being detected in previous MRI. Sonography **B** demonstrates a good visualization of the HCC as a hypoechogenic mass (arrows) and is easily punctured (arrow 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).

tients, 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 modality 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.

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Publikation 9

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 Dec;10(6):516-521. doi: 10.5114/jcb.2018.80626.

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

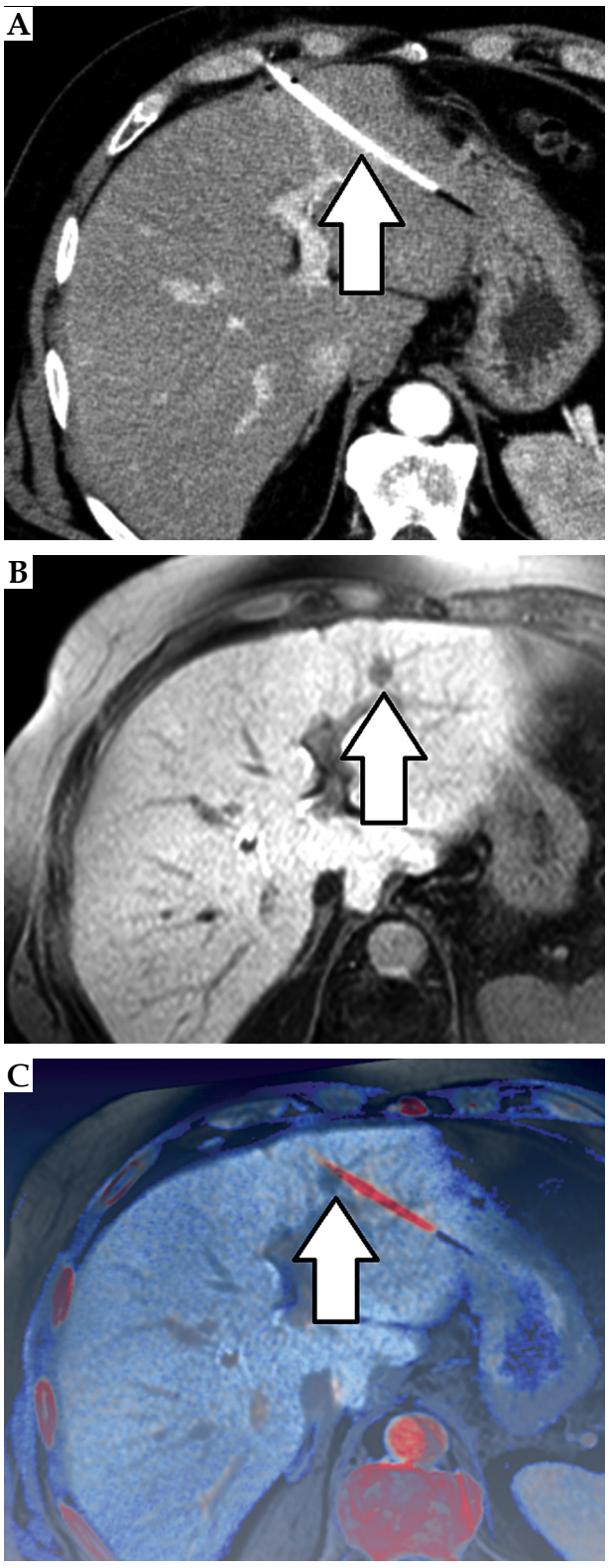

Fig. 1. Image fusion data set: peri-interventional CT showing HDR brachytherapy catheter (arrow, **A**), follow-up MRI suspecting a needle track lesion (arrow, **B**), axial image fusion of follow-up MRI and planning CT of HDR brachytherapy confirming the origin of the new lesion within the former path of the brachytherapy catheter (arrow, **C**)

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.

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.

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Publikation 10

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

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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

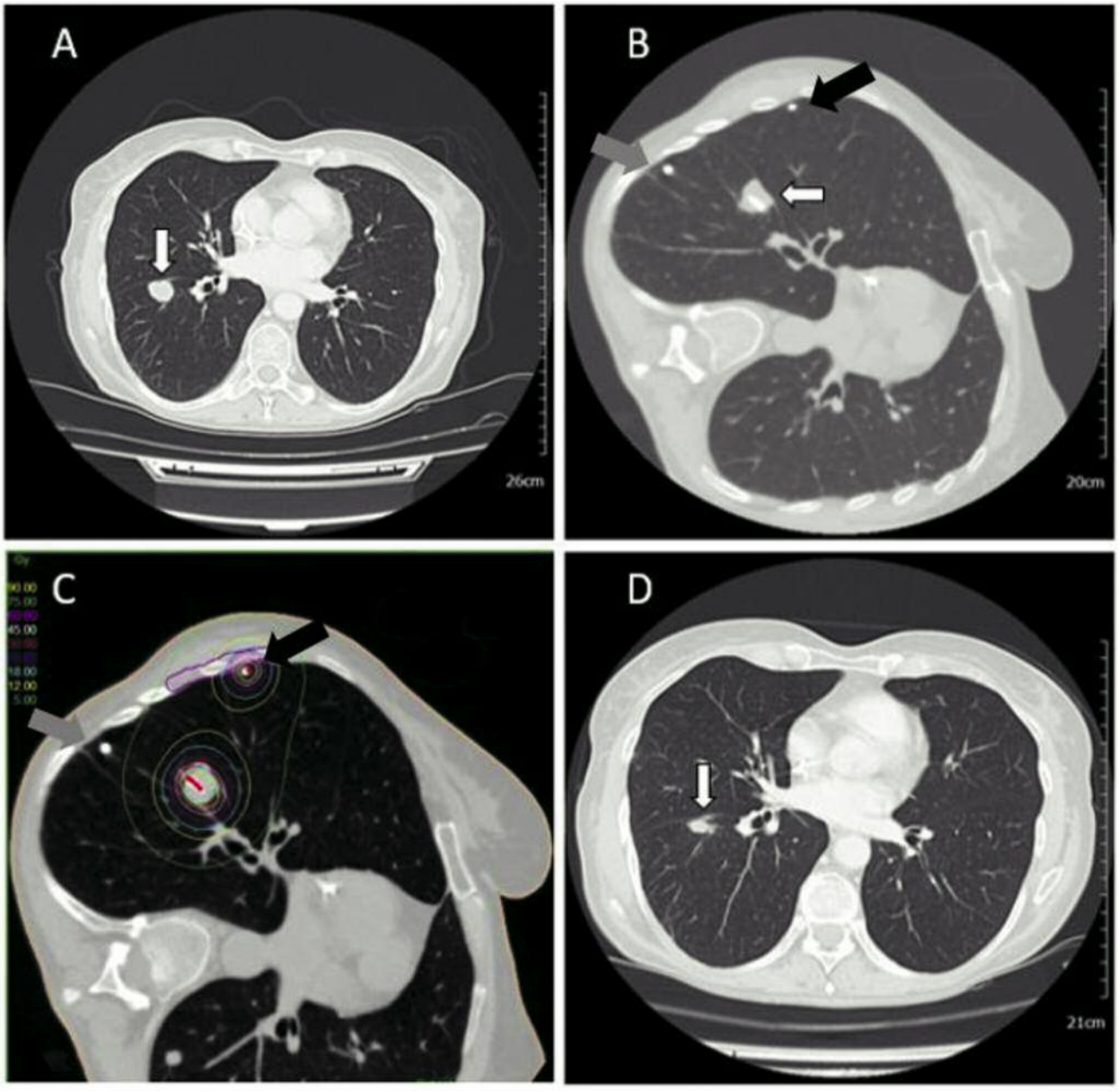

Figure 1. *Interventional technique and local tumor control in patient 1 with metastatic anal squamous cell carcinoma (ASCC). A: Pre-interventional contrast-enhanced computed tomographic (CT) slice showing a metastasis of ASCC (white arrow) in the lower lobe of the right lung. The second clinical target 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

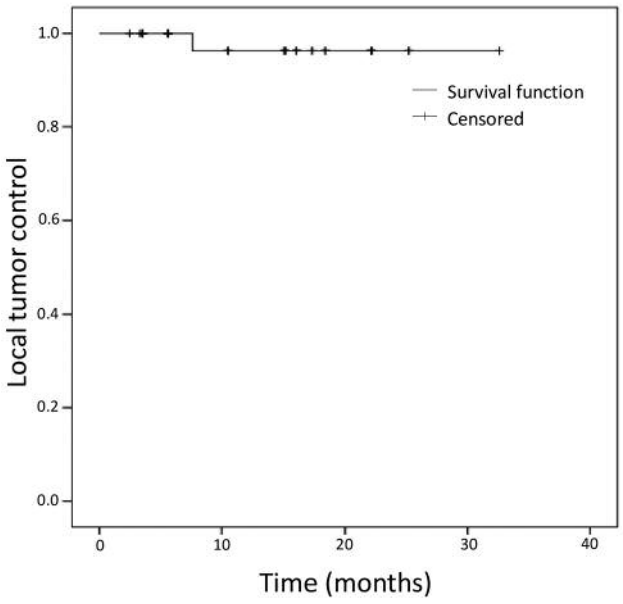

Figure 2. *Kaplan–Meier curve for local tumor control after interstitial brachytherapy.*

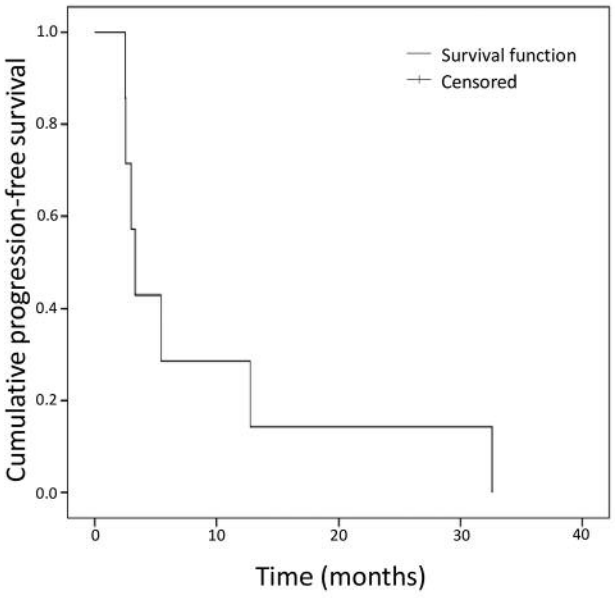

Figure 3. *Kaplan–Meier curve for progression-free survival after interstitial brachytherapy.*

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

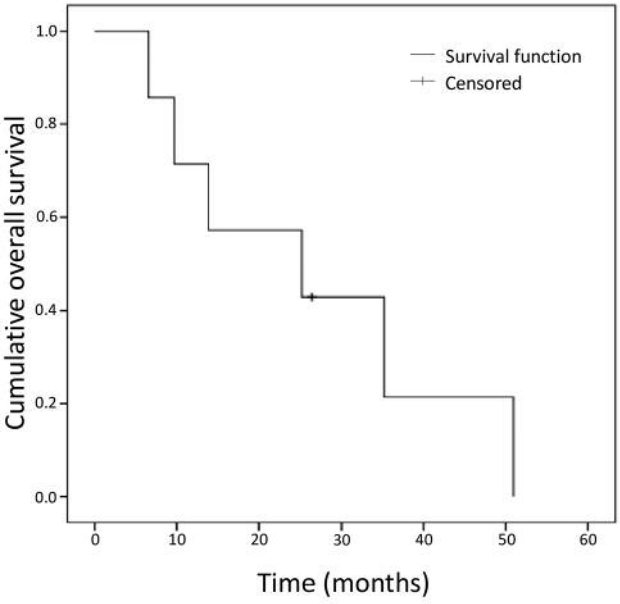

Figure 4. *Kaplan–Meier curve for overall survival of six patients treated with interstitial brachytherapy. At the date of censoring, patient 1 was still alive.*

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.

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Publikation 11

Treatment of hepatic pancreatic ductal adenocarcinoma metastases with high-dose-rate, image-guided interstitial brachytherapy: a single center experience.

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Original paper

Treatment of hepatic pancreatic ductal adenocarcinoma metastases with high-dose-rate image-guided interstitial brachytherapy: a single center experience

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Abstract

Purpose: To evaluate the efficacy and safety of image-guided (computed tomography/magnetic resonance imaging – CT/MRI) high-dose-rate (HDR) interstitial brachytherapy (iBT) as a salvage maneuver for the treatment of hepatic metastases originating from hepatic pancreatic ductal adenocarcinoma (PDAC). PDAC metastases present a major and unresolved problem, and any surgical approach or local therapeutic intervention remains extremely controversial.

Material and methods: A cumulative number of 45 hepatic PDAC metastases in 16 patients were treated and retrospectively analyzed. Synchronous metastatic spread was observed in five patients, metachronous in eleven. 14 patients had resection of the pancreatic primary prior to iBT: eight Whipple/PPPD and six distal pancreatectomy procedures. The hepatic metastases were progressing under chemotherapy, thus iBT was applied as a salvage maneuver with the intention of local tumor control and prolonged survival. iBT is applied interstitially, with temporarily introduced ^{192}Ir source in a single fraction HDR irradiation regime to eradicate vital tumor cells. Response to treatment was assessed clinically with CT/MRI every three months.

Results: Local tumor control was achieved in 87% of all treated metastases. The median diameter of the irradiated lesions was 2.2 cm (range, 1-11.2 cm), the median irradiation dose was 21 Gy (range, 5-29.1 Gy). Median progression-free survival (PFS) after iBT was 3.4 months (range, 1.5-19.6 months), the median overall survival (OS) after iBT was 8.9 months (range, 3.1-29.3 months). Three major complications (CTCAE grade 3) occurred following iBT: three cases of liver abscess, which were successfully resolved with drainage and antibiotics.

Conclusions: Overall, iBT is a safe procedure, which enables excellent rates of local tumor control and presents a viable anti-neoplastic treatment option as a salvage therapy for metastatic PDAC patients.

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Key words: PDAC, interstitial brachytherapy, local ablation, local tumor control, salvage.

Purpose

Pancreatic cancer is the fourth most fatal cancer in both women and men, with a life expectancy of 2-5% at 5 years [1,2]. Moreover, most patients have already progressed to an advanced or metastatic stage of the disease at the time of diagnosis. Several preclinical studies established that pancreatic ductal adenocarcinoma (PDAC) is a systemic disease from the outset, displaying early micrometastatic spread [3,4]. Autopsy studies of primary resected PDAC patients showed that 70-85% of patients die of systemic recurrence rather than local disease [5].

Only 10-15% of all patients are eligible for surgery, which is presently considered to be the only potentially curative approach [6,7]. Even after surgery, PDAC remains highly lethal, as many patients develop hepatic metastases. Resectability status mainly depends on peripancreatic vessel contact/infiltration and presence or absence of distant metastases [8]. However, many PDAC patients undergo surgery of the primary tumor at some point and consequently have a biliodigestive anastomosis (BDA), which ultimately results in bacterial colonization of the intrahepatic bile ducts and complicating any hepatic metastasis treatment [9].

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Treatment of PDAC metastases is challenging, since partial hepatectomy as a principal method not only failed to show any promising results, but also cannot usually be performed repeatedly due to impairment of liver function and the patient's general condition [10,11]. Alternative measures like thermal liver ablation (RFA, laser therapy), are often complicated by cholestasis, bile duct strictures, and hepatic abscesses, with even higher incidence rates after previously performed BDA [12]. Even though being minimal invasive, thermal ablation measures underlie several restrictions such as tumor size (< 5 cm), heat sink effect, and inability to be used near thermosensitive structures.

In contrast to the aforementioned therapies, image-guided high-dose-rate brachytherapy (iBT) presents a different, anti-neoplastic, transcutaneous, and minimally invasive treatment option, and is applied in this study. Its efficacy and ability to provide local tumor control (LTC) has been proven by several investigators for different tumor entities in the past, achieving excellent local tumor control rates around 90% [13,14,15,16]. iBT is an afterloading technique that employs a ^{192}Ir source, which is placed temporarily into the clinical target volume, i.e. the tumor. High-dose-rate irradiation is applied in a single fraction, providing an extensive cytotoxic effect via DNA and RNA damage to eradicate vital tumor cells. Other researchers examined the use of iBT for the treatment of patients with PDAC liver metastases and demonstrated a high local tumor control rate of 91% [17].

The goal of our study was to assess the efficacy and safety of iBT as a salvage maneuver for the treatment of liver metastases originating from PDAC.

Material and methods

Patient characteristics

Sixteen patients, with histologically proven PDACs and a cumulative number of 45 unresectable liver metastases, received treatment with iBT in our department between February 2010 and March 2017, and were enrolled in this retrospective study. Every patient was in a metastatic and progressive stage of disease at the time of referral to our department. Our study was approved by the local ethics committee.

Study design and eligibility criteria

Local tumor control (LTC) and overall safety of iBT were the primary endpoints of this retrospective study.

Each individual PDAC patient's case was discussed at an interdisciplinary board of oncologists, interventional radiologists, radiation oncologists, and visceral surgeons who determined the indication for iBT for each patient individually.

The inclusion criteria were: 1) Resection impossible or unfavorable due to perioperative risk or loss of liver function; 2) Patient unwilling to undergo surgery, 3) Oligometastatic (≤ 5 metastases upon initial presentation)/ controllable disease extent; 4) Adequate coagulation parameters (thrombocytes > 50000/nl, prothrombin > 50%, partial thromboplastin time < 50 s). Exclusion criteria were correspondingly: 1) Lack of consent, and 2) Uncontrollable tumor spread.

Interventional technique and irradiation

Prior to the iBT procedure, a whole-body contrast-enhanced CT and a Gb-EOB-DTPA-enhanced liver MRI (Primovist, Bayer Pharma, Leverkusen, Germany) were acquired for treatment planning and staging purposes. Physical status and laboratory parameters were also evaluated.

During and prior to the intervention, analgesia (fentanyl), sedation (midazolam), and local anesthesia (lidocaine) were administered. An 18-gauge needle was used under CT fluoroscopic guidance (Toshiba, Aquilion, Japan) or real time 1.0 Tesla MRI (Panorama 1.0T, open MR system, Philips Healthcare) to puncture the target lesions. In a next step, a flexible 6-French catheter sheath (Radifocus, Terumo^{TM}) was placed using Seldinger technique over a stiff angiography guidewire (Amplatz, Boston Scientific, Marlborough, USA). Finally, the 6-French afterloading catheter (Afterloadingkatheter, Primed Medizintechnik Gmbh, Halberstadt, Germany) was introduced and the catheter ending temporarily fixated to the skin with sterile bandages and a cutaneous suture. Target lesion size and nearby structures at risk determined the number of catheters and their angulation. A CT scan in breath-holding technique or a Gadolinium-enhanced MRI were acquired for further treatment and irradiation planning as well as for catheter positioning confirmation. The interventional radiologist and the radiotherapist marked the clinical target volume and the adjacent organs at risk in every CT or MRI slice.

The irradiation design was devised employing the acquired dataset and the software system Oncentra (Nucletron, Elekta Ab, Stockholm, Sweden). The software was a part of the HDR afterloading system. The three-dimensional coordinates (x, y, z) of each positioned catheter's tip in relation to the tumor margins were transferred into the treatment planning system. Furthermore, the calculated isodose lines were inspected in every imaging slice and adapted to the target lesion margins. An imaging example of the interventional technique is illustrated in Figure 1.

The afterloading/iBT system (Nucletron, Elekta Ab, Stockholm, Sweden) applied an ^{192}Ir source with a nominal activity of 10 Ci (370GBq). The irradiation was administered in a single fraction. The reference dose was defined as 20 Gy to enclose the entire target lesion (D99.9%); even higher, exponentially increasing doses were applied at the target lesion's irradiation center. Prevention of new peripheral tumor incidences was achieved through implementation of a 5-millimeter security margin around the target lesion, i.e., the clinical target volume (CTV). Adjacent organs at risk such as the gastrointestinal tract (GI) were respected, and the irradiation scheme and dose correspondingly adjusted (empiric GI tract dose < 14 Gy/ml) [18].

Upon completion of the iBT procedure, the catheters were removed. The puncture sites were sealed by injection of gelfoam or fibrin tissue glue.

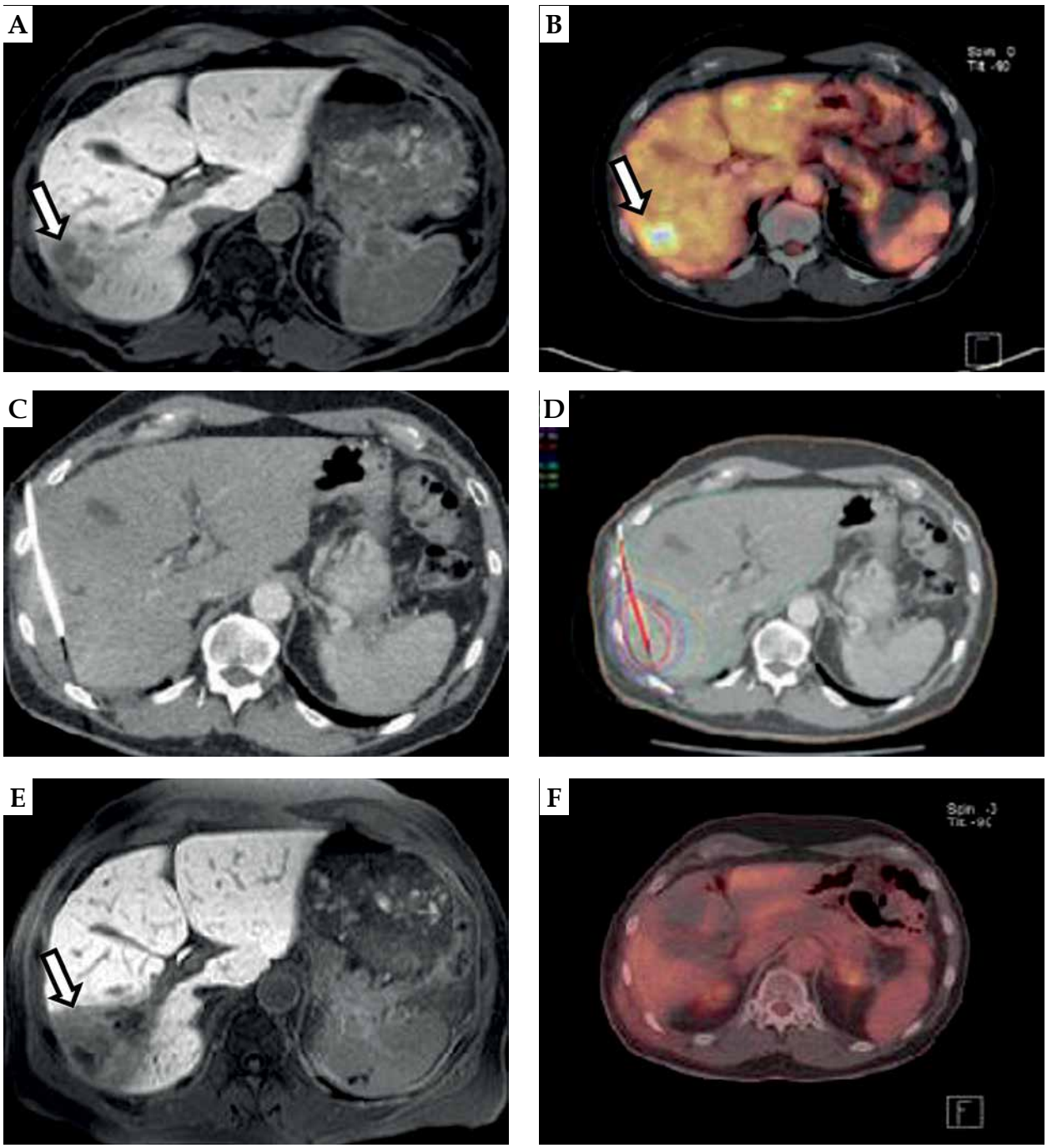

Fig. 1. Local tumor control in a patient with metastatic PDAC. **A**) Axial T1w Gd-EOB-DTPA (Primovist)-enhanced MRI (baseline MRI prior to iBT), arrow points to liver metastases; **B**) FDG-PET-CT demonstrates the activity of the hepatic lesions (arrow) prior to iBT; **C**) Inserted brachytherapy catheter in the liver lesions (white arrow) during CT-guided iBT; **D**) Colored lines represent the irradiation isodoses, with red line showing 20 Gy; **E**) Axial T1w Gd-EOB-DTPA-enhanced follow-up MRI after iBT with Gd-EOB-DPTA enhancement defect following irradiation; **F**) FDG-PET-CT (follow-up) shows no activity in the hepatic ablation area

Follow-up

Response to iBT treatment was evaluated every three months after the ablation procedure: a Gb-EOB-DTPA-enhanced liver MRI, a contrast-enhanced CT (thorax and abdomen), clinical and laboratory evaluations were performed. Changes in size and enhancement defects were correlated in a dynamic T1w GRE sequence, DWI/ADC, post-Gd-EOB-DTPA, and a T2w sequence. Tumor edema was visualized in a T2w sequence, vital tumor tissue in DWI and late enhancement (post-radiation) defects in the post-Gd-EOB-DTPA sequence and the contrast agent dynamic sequences. Measurements were ultimately made in axial slices of the post-Gd-EOB-DTPA sequence in cor-

relation with the DWI to account for vital tumor tissue and to differentiate from late enhancement defects. In some cases, an FDG-PET-CT was acquired.

Adverse events were recorded and defined corresponding to the Common Terminology for Adverse Events (CTCAE), version 4.03.

Local tumor control (LTC) after brachytherapy was defined corresponding to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) categories as stable disease (SD), partial remission (PR), and complete remission (CR). Progressive disease was defined as an increase of tumor diameter > 20% during follow-up.

Statistical methods

The primary objectives of this retrospective, single arm study were local tumor control and the overall safety of iBT. Progression-free survival and overall survival were secondary objectives. Calculations of LTC, PFS, and OS were done using Kaplan-Meier method with SPSS version 22 (SPSS, version 22.0; SPSS, Chicago Illinois).

Results

Sixteen patients with histologically proven PDAC, having a cumulative overall amount of 45 liver metastases, were treated with iBT in our department between 2010 and 2017, and were included in this retrospective study (Table 1). The median patient age at the time of diagnosis was 62 years (range, 35-73 years). Localization of the pancreatic primary tumor was as follows: nine in the head, six in the tail, and one in the body. Fourteen patients had a resection of the primary tumor prior to iBT: eight cases of Whipple/PPPD procedure and six cases of distal pancreatectomy. One patient's primary was treated with iBT instead of surgery. Only one patient neither had resection nor iBT of the primary.

Table 1. Patients characteristics

Total number of patients	16
Sex	
Men	10
Women	6
Age at time of diagnosis	
Median	62 (Q_1 = 55, Q_3 = 69)[1]
Range	35-73
Primary localization	16
Caput (head)	9
Cauda (tail)	6
Corpus (body)	1
Chemotherapy (before iBT)[2]	16
Resection of the primary (before iBT)	14/16
Whipple & PPPD	8
Distal pancreatectomy	6
Other therapies	
Partial hepatectomy & radiation	1
SIRT	1
IBT primary (no resection)	1
ERCP (caput primary)	3
Metastases (cumulative)	45
Liver	45
Type of metastatic spread	
Synchronous	5
Metachronous	11
Lesion size (max diameter in cm)	
Median	2.2 (Q_1 = 1.3, Q_3 = 3.3)
Range	1-11.2
Irradiation dose (iBT) (Gy)	
Median	21 (Q_1 = 17, Q_3 = 24)
Range	5-29.1
Irradiation time (iBT) (min)	
Median	29.8 (Q_1 = 13.7, Q_3 = 38.3)
Range	8-82.8
Number of catheters/lesion	
Median	1 (Q_1 = 1, Q_3 = 2)
Range	1-6
Local tumor control	39/45 (86.7%)
Local tumor control time (months)	
Median	3.3 (Q_1 = 2.8, Q_3 = 5.5)
Range	1.5-27.9
Progression-free survival (months)	
Median	3.4 (Q_1 = 2.8, Q_3 = 6.5)
Range	1.5-19.6
Overall survival after iBT (months)	
Median	8.9 (Q_1 = 5.6, Q_3 = 8.9)
Range	3.1-29.3
OS from time of diagnosis (months)	
Median	27.5 (Q_1 = 19.5, Q_3 = 51.3)
Range	13-63
Previous treatment (before iBT)	
Chemotherapy	16 (100%)
Resection	14 (87.5%)
Selective internal radiotherapy	1
IBT primary (no resection)	1
IBT image guidance	
CT	26
MRI	19
Time of hospitalization (days)	
Median	4
Range	3-6

[1]quartile range, [2]image-guided high-dose-rate interstitial brachytherapy
Whipple & PPPD – whipple procedure and pylorus preserving pancreaticoduodenectomy, SIRT – selective internal radiotherapy (radioembolization), ERCP – endoscopic retrograde cholangiopancreatography

Table 2. Organs at risk and tumor dose overview

	D1 cc Median (range)	V_5 Gy (%)	D_{90}	$D_{99.9}$	D_{mean}
Gastr (*n* = 7)	8.1 (4.4-16.4)	X	X	X	X
Duod (*n* = 1)	X	X	X	X	X
Colo (*n* = 3)	8 (4.7-19.8)	X	X	X	X
Kidn (*n* = 4)	16 (12.1-21.2)	X	X	X	X
Heart (*n* = 4)	13.4 (1.9-18.1)	X	X	X	X
Liver	X	20 (1.5-70)	X	X	X
Tumor (*n* = 45)	X	X	31.5 (15.5-81)	21.1 (11.5-62)	20 (1.5-70)

Table 2 shows 5 Gy liver volume %, the organs at risk (OARs) dose (Gy/ml), the tumor doses D_{90}, $D_{99.9}$, and D_{mean} (Gy) in median and range. A cumulative number of 26 brachytherapy interventions were performed. The n = ... states the number of interventions were each organ was at risk, e.g. gastr n = 7 – gastric organ at risk in 7 out of 26 interventions (in 19 interventions $D_{1\,cc}$ of 0 Gy/ml)

Synchronous metastatic spread was observed in five patients and metachronous spread in eleven patients.

Every patient received some form of palliative chemotherapy and showed disease progression prior to iBT: gemcitabine was administered to twelve patients and FOLFIRINOX to four patients. Gemcitabine monotherapy was amended in some cases: two cases of additional erlotinib, three cases of additional paclitaxel and two cases of additional oxaliplatin.

In the recent follow-up staging CT before referral to our department, every patient's PDAC disease was found to be progressive under palliative chemotherapy; hence, iBT was applied as a salvage maneuver and chemotherapy discontinued four weeks prior to the iBT procedure. Disease progression was the primary reason for chemotherapy cancellation and drug-related toxicity was the secondary reason. Some patients received repeated iBT treatments, either to split the treatment and irradiation burden into two or more sessions, or to treat newly developed metastases later. A more detailed overview of the performed iBT and the dose applied is presented in Table 2.

Treatment characteristics

The median tumor diameter was 2.2 cm (range, 1-11.2 cm). The number of inserted catheters per lesion during iBT varied between one and six, with a median of one. CT guidance was used in 26 interventions, MRI guidance in 19. The minimal planned/anticipated tumor enclosing dose was 20 Gy (D99.9%), which had to be adapted in some cases due to risk structures in proximity – a median irradiation dose of 21 Gy (range, 5-29.1 Gy) was administered. The median total irradiation time was 29.8 minutes (range, 8-82.8 minutes).

The intended tumor enclosing dose (D99.9%) was reached in 35 of 45 (77.7%) of all treated metastases. For the treatment of the other 10 lesions, the dose had to be adjusted due to risk structures in proximity.

The time of hospitalization ranged between three and six days, with a median of four days. Three patients developed a liver abscess (CTCAE grade 3) following an iBT session, which was successfully resolved with transcutaneous drainage and antibiotics, each without significant hospitalization prolongation. Four other patients received prophylactic periinterventional antibiotics as a precaution due to pre-existing, considerable cholestasis; no sign of infection or liver abscess was observed.

Local tumor control, overall survival, progression free survival

Local tumor control was achieved in 87% of all treated lesions in the Kaplan-Meier analysis (Figure 2). A cumulative number of six local relapses (liver metastases) were observed in four patients; one patient had a relapse of every treated lesion (three in total). The median progression-free survival (PFS) was 3.4 months (Figure 3). The median overall survival of the 16 patients with metastatic PDAC, calculated from the time of iBT was 8.9 months (Figure 4). The median OS from the time of PDAC diagnosis was 27.5 months.

Discussion

PDAC mortality rates and OS remain poor and have barely improved in the last decades; median overall sur-

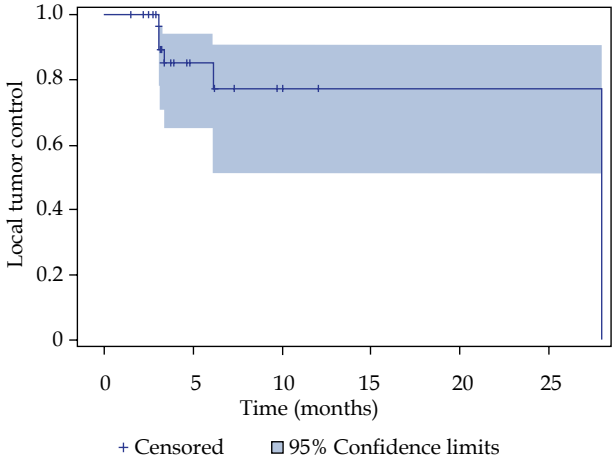

Fig. 2. Local tumor control (LTC) after iBT of pancreatic ductal adenocarcinoma (PDAC) metastases, estimated with the Kaplan Meier method

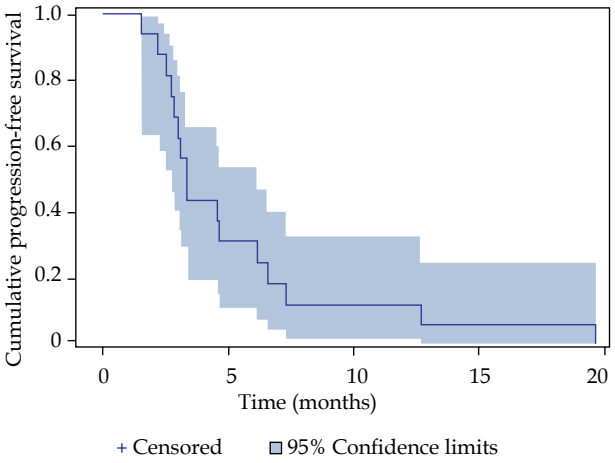

Fig. 3. Progression-free survival (PFS), calculated from the time of iBT, of patients with metastatic PDAC after treatment with iBT, estimated with the Kaplan Meier method

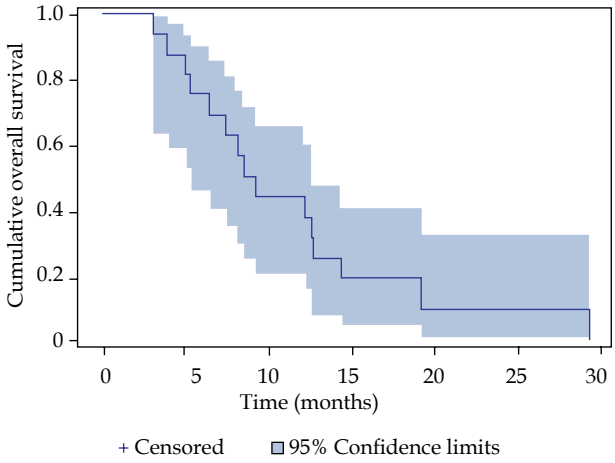

Fig. 4. Overall survival (OS), calculated from the time of iBT, of patients with metastatic PDAC ablated with iBT, estimated with the Kaplan Meier method

vival (mOS) across various studies is still less than two years, mOS of metastatic PDAC is about 6 months [19]. However, two RCTs established recent breakthroughs in first line chemotherapy with FOLFIRINOX (OS, 11.1 months) and the combination of gemcitabine and nab-paclitaxel (OS, 8.5 months) compared with the traditional gemcitabine monotherapy (OS, 6.8 months) [20,21]. The downside of these "new" first line regimens is their limited applicability. The administration is reasonable only to patients with an ECOG PS of 0 or 1, which is the case for about 10-15% of all PDAC patients. In our study, four patients (25%) initially had an adequate ECOG PS and received FOLFIRINOX. An ECOG PS of 2 limits the options to gemcitabine monotherapy according to guidelines, which was the case for other 12 patients in our study.

Results from randomized trials comparing chemotherapy with chemotherapy plus conventional external radiation indicate no significant survival improvement with additional radiation [22].

The current standard of care for early-stage disease is surgery followed by adjuvant chemotherapy. Although surgical resection is widely considered curative, observed outcomes across various studies fail to support that presumption. A large analysis of more than 300,000 patients from the National Cancer Database demonstrated that mOS after resection of the primary was only 13 months [23]. Other large RCTs and trials support that data: mOS was less than 2 years [19,24,25]. The 30-day mortality after PDAC resection was up to 9% [19,24].

No treatment consensus exists regarding metastatic PDAC, which is considered unresectable based on the NCCN guidelines, apart from systemic therapy. While surgical metastasectomy being the standard method of choice for other cancer entities like colorectal cancer (CRC) or neuroendocrine liver metastases, the surgical approach fails to provide comparable promising results for PDAC metastases. The oncological value of liver surgery in PDAC patients is still highly questionable. Therefore, synchronous pancreatic and liver resections are only performed in very few PDAC cases, even in high-volume centers. A small study examined the outcome of seven patients after liver metastasectomy and published a mOS of 5.8 months [26]. Klempnauer *et al*. [26] reported a mOS of 8.3 months after synchronous liver and pancreatic resection and 5.8 months after metachronous hepatic resection. Klein *et al*. [27] published a mOS in a study (n = 22) of PDAC patients with synchronous hepatic metastasis resection of 7.6 months after surgery. Gleisner *et al*. [28] reported a mOS of 6 months even among highly selected patients with a low-volume metastatic liver disease. No benefit in overall survival was found in an older study by Takada *et al*. [29].

In contrast, the OS of our study calculated after iBT was 8.9 months, which is quite remarkable considering that all our patients had no further therapeutic options and were progressing under palliative chemotherapy, which was cancelled four weeks prior to iBT procedures. Furthermore, many of our patients had an unfavorable ECOG PS of 2, which rendered any surgical approach impossible. Re-challenge with alternative systemic anti-neoplastic regimens was either prohibited by the overall clinical condition or failed. To our knowledge, there is no comparable study evaluating the OS after resection of PDAC liver metastases in a salvage situation.

Another treatment approach for PDAC liver metastases are minimal invasive treatments like radiofrequency ablation. Park *et al*. came to the conclusion that selected patients with single, small sized (< 2 cm) PDAC liver metastases gain a survival benefit through an application of RFA [30]. However, certain restrictions of thermal ablation methods like RFA limit its applicability; tumor size < 5 cm, heat sink effect adjacent to vessels, high tumor vascularization, and proximity to central bile duct are the most important limitations.

In contrast, these restrictions do not apply to iBT, no size limit or cooling effects concerning brachytherapy are known. IBT even surpasses the size limit of 6 cm of stereotactic body radiation therapy (SBRT) and seems to induce fewer cases of radiation-induced liver disease (RILD) [31]. An advantage of local ablation measures like iBT or RFA concerning liver metastases is that it can be performed re-

peatedly while preserving liver function. The issue of potential needle track metastasis was addressed specifically by radiation of the interventional access as a precaution.

The results of our study (mOS 8.9 months, PFS 3.4 months, LTC 87%) confirm the data published by Wieners *et al*. (mOS 8.6 months, PFS 3.2 months, LTC 91%) [17]. The observed complication rate is also similar; we report three major complications in 45 iBT procedures, whereas Wieners *et al*. also report three major complications in 49 iBT procedures – in both studies with hepatic abscesses. A crucial risk factor promoting liver abscess caused by ascending biliary infection based on bacterial colonization is a biliodigestive anastomosis (BDA) in patients with prior Whipple procedures. Correspondingly, the three cases with hepatic abscesses in our study, which were successfully resolved with drainage and antibiotics, also had a BDA following resection of the pancreatic head. According to literature, major adverse events (grade 3 and 4) after iBT are observed in about 3% of cases [32].

Despite the promising results, limitations of our study are the relatively small patient collective and the retrospective, single arm design. The outcome of our study, however, substantiates the findings of Wieners *et al*. suggesting that iBT might prolong OS in a metastatic setting, which generally implies dreadful prognosis. Further investigations in prospective RCTs are necessary to validate the results of our small, retrospective analysis. Until then, the current treatment rationale should be to identify eligible patients for local treatment options in combination with systemic chemotherapy to prolong survival.

Conclusions

Our study demonstrates and confirms that iBT is an overall safe procedure for the treatment of PDAC liver metastases and excellent local tumor control rates can be achieved.

Disclosure

Authors report no conflict of interest.

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Publikation 12

Efficacy and safety of percutaneous CT-guided high-dose-rate interstitial brachytherapy in the treatment of oligometastatic lymph node metastases of the retroperitoneal space.

Heinze C, **Omari J**, Manig M, Hass P, Venerito M, Damm R, Jargiello T, Ricke J, Powerski MJ, Pech M.

J Contemp Brachytherapy (noch nicht in Pubmed veröffentlicht)

Original paper

Efficacy and safety of percutaneous computed tomography-guided high-dose-rate interstitial brachytherapy in treatment of oligometastatic lymph node metastases of retroperitoneal space

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Abstract

Purpose: To assess efficacy, safety, and outcome of computed tomography (CT)-guided high-dose-rate (HDR) interstitial brachytherapy in patients with oligometastatic lymph node metastases of the retroperitoneal space.

Material and methods: Twenty-four patients with a total of 47 retroperitoneal lymph node metastases from different primary tumors were treated with CT-guided interstitial brachytherapy using an ^{192}Ir source (single fraction irradiation). Every three months after treatment, clinical and imaging follow-up were conducted to evaluate local control and safety.

Results: Median follow-up was 9.6 months (range, 2.9-39.0 months). Local tumor control rate was 95.7%. The median diameter of the gross tumor volume was 2.2 cm (range, 1-8.6 cm), treated with a median D_{100} (minimal enclosing tumor dose) of 14.9 Gy (range, 4.5-20.6 Gy). One severe adverse event (grade three) was recorded.

Cumulative median progression-free survival was 4.2 months (range, 1.4-23.7 months), and cumulative median overall survival after interstitial brachytherapy was 15.9 months (range, 3.8-39.0 months).

Conclusions: CT-guided HDR interstitial brachytherapy is a safe and feasible method for local ablation of oligometastatic lymph node metastases of the retroperitoneal space, and might provide a well-tolerated additional therapeutic option in the multidisciplinary management of selected patients.

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Key words: lymph node metastases, image-guided intervention, radiation therapy/oncology, interstitial brachytherapy.

Purpose

Almost all types of solid cancer have the potential of lymphatic dissemination to the retroperitoneal space, especially squamous cell carcinoma of the pelvis, urinary or gynecological system as well as gastrointestinal adenocarcinoma or renal cell carcinoma [1]. Therapeutic options depend on the type of primary tumor, location, and number/volume of the retroperitoneal lymph node metastases (rLNM), and on the patient's performance status. However, little is known about the impact of the oligometastatic state in these patients. The term 'oligometastases' was coined by Hellmann *et al.* in 1995; the authors hypothesized that the process of cancer metastases develop along a continuum from locally limited to polymetastatic disease and therefore, over time, malignant cells acquire widespread metastatic potential [2]. Furthermore, they suggested that selected patients with a restricted metastatic capacity could be classified into a specific intermediate transitional stage between single metastasis and polymetastatic disease. Nowadays, precise clinical definitions vary among publications. In general, oligometastatic disease is defined by metastases that are limited in number (typically less than five) and location, but more importantly are amendable for regional treatment, aim-

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ing for a complete resection/ablation [3,4,5]. In general, metastatic malignancies are associated with a poor prognosis and (according to the current standard of care) primarily treated with systemic chemotherapy or molecular targeted therapy. However, in the described model, local tumor control would have a potential to decelerate cancer progression or yield systemic control. Furthermore evidence exists that patients with oligometastases can even be cured by resection of the lesions, i.e. most frequently reported in patients with colorectal carcinoma after resection of liver metastases [6,7].

Table 1. Patients characteristics

Variables	
Total number of patients (*n*)	24
Patient sex	
Men	13
Women	11
Age at time of diagnosis (years)	
Median	55.5
Range	29-81
Primary tumor entity: number of patients/total number of lesions per entity (*n*)	
Colorectal carcinoma	5/7
Cholangiocellular carcinoma	4/7
Renal cell carcinoma	3/7
Pancreatic ductal adenocarcinoma	3/5
Hepatocellular carcinoma	2/4
Ovarian cancer	2/2
Cancer of unknown primary	2/5
Malignant pheochromocytoma	1/4
Malign melanoma	1/3
Urothelial carcinoma	1/3
Distant metastasizing	
Synchronous	9
Metachronous	15
Number of lesions (*n*)	47
Maximum diameter (cm)	
Median	2.2
Range	1.0-8.6
Lesions per patient (*n*)	
Median	2
Range	1-4
Administered D_{100}; range (Gy)	
Median	14.9
Range	4.5-20.6
Follow-up time (months)	
Median	9.6
Range	2.9-39.0

However, retroperitoneal lymph node dissection is a surgical challenge, especially in a post-chemotherapeutic setting with significant morbidity [8]. Alternative less invasive local treatments include stereotactic body radiation (SBRT), radiofrequency ablation (RFA), and image-guided high-dose-rate interstitial brachytherapy (HDR-iBT = iBT). Out of the toolbox of local ablation techniques, iBT is a relatively new technique, where an iridium 192 (^{192}Ir) source is temporarily introduced into the metastatic lesions via percutaneously implanted applicators, which are placed under imaging guidance in a minimal invasive intervention; therefore, enabling a clearly delineated single fraction irradiation of the target volume. iBT has already been shown to be a gentle treatment with a minimum of complications in ablation of primary or secondary malignancies at various sites, e.g. colorectal cancer or hepatocellular carcinoma [9,10,11,12]. To our knowledge, no data has been published so far evaluating the efficacy of iBT in the treatment of rLNM. In this study, we retrospectively analyzed safety and efficacy in a cohort of 24 patients with 47 rLNM who underwent CT-guided iBT.

Material and methods

Eligibility criteria and patients

Patient recruitment was carried out between March 2015 and March 2017. We retrospectively included 24 patients (13 male and 11 female; median age, 55.5 years; range, 29-81 years) with 47 rLNM. All patients were diagnosed with different types of primary tumors, all histologically proven (for detailed patients characteristics see Table 1).

All patients displayed tumor progression at the time of referral to our clinic and every case was discussed in an interdisciplinary tumor board. Furthermore, inclusion criteria were as follow: a) Technically unresectable metastases, assessed by a surgeon with expertise in the field of visceral surgery; b) Medical contraindication for resection or severe comorbidities; c) Refusal of surgery; d) Patients considered unfit for chemotherapy or lack of chemotherapy options; e) Refusal of chemotherapy; f) The East Coast Oncology Group (ECOG) performance status below two; g) Platelet count > 50,000/nl, international normalized ratio (INR) ≥ 1.5, partial thromboplastin time < 50 seconds. No upper limit concerning maximum tumor diameter or number of lesions was placed; however, all lesions had to be amenable for regional treatment aiming for a complete ablation. Contraindications for local ablation included: a) Peritoneal carcinomatosis; b) Prognosis limiting, widespread systemic disease; c) Lack of consent.

Prior to ablation, 17 out of 24 patients were treated with systemic treatment including immunotherapy. Sev-

en patients did not receive any chemotherapy due to reduced general condition, comorbidities, or refusal of systemic treatment. All, except two patients, underwent resection of the primary tumor or metastatic lesions, including local ablation using iBT, RFA, or microwave ablation (MWA) of liver, lung, or lymph nodes.

Prior to iBT of rLNM, all patients underwent a full clinical status evaluation with a physical examination and laboratory assessment. Additionally, a whole-body contrast-enhanced CT was performed to obtain a complete staging. A positive vote of the ethics committee for the analysis of the patient data was received, and informed consent was obtained from all individual participants included in the study.

Interventional technique and irradiation

The technique has been described elsewhere in detail [10,13,14]. In short, under guidance of a fluoroscopy-CT (Toshiba, Aquilion, Japan), an 18-gauge needle was introduced into the target lesions and a flexible 6F catheter sheath (Radifocus, Terumo™ Introducer II, Terumo Europe, Leuven, Belgium) was inserted over a stiff angiography guide wire using Seldinger's technique. Thereafter, the angiographic guidewire was removed and replaced by a 6F afterloading catheter (Afterloadingkatheter, Primed® Medizintechnik GmbH, Halberstadt, Germany). The interventional procedure was performed under local anesthesia (lidocaine) and analgosedation (midazolam and fentanyl). The number and arrangement of the implanted 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 was obtained to document correct catheter positioning and to plan irradiation. On these images, the target volume was drawn precisely as gross tumor volume (GTV) and clinical target volume (CTV); additionally, organs at risk (OARs) such as duodenum or spinal cord were outlined by an interventional radiologist and radiation oncologist. The ends of the afterloading catheters were secured to the skin with a suture and the tip of the catheter was presumably in a fixed position; therefore, planning target volume (PTV) and CTV are in accordance with one another. Dose calculation was performed using the acquired dataset with Oncentra-Masterplan (Oncentra® Brachy treatment planning system, Elekta AB, Stockholm, Sweden) and the calculated isodose lines, relative to the CTV, were controlled and adapted slice by slice. All irradiations were administered as single fraction irradiations using an ^{192}Ir source with a nominal activity of 10 Ci. Depending on the histological type of the primary tumor, a reference dose of 15-20 Gy was prescribed to our patients (e.g. 15 Gy for renal cell carcinoma and hepatocellular carcinoma, 20 Gy for cholangiocellular carcinoma, malignant pheochromocytoma). The reference dose was defined as the minimum dose enclosing the complete CTV (D_{100}). There was no limitation regarding higher doses inside the tumor volume. However, depending on adjacent OARs, dose limitations were taken into account, i.e. gastric mucosa (< 15.5 Gy/ml) [15]. After irradiation, the catheters were removed and the puncture channels were sealed using thrombogenic material (Gelfoam®; Pfizer Inc., New York, US). Figure 1 illustrates the interventional technique.

Follow-up

Every three months after iBT, clinical laboratory and imaging follow-up (contrast-enhanced whole-body CT) were performed. Local tumor control (LTC) and progression-free survival (PFS) were assessed by employing RECIST criteria (RECIST version 1.1). LTC was defined as decreasing or stable presentation of the target lesion after iBT. PFS was defined as LTC without tumor progression at any other side 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).

Study design and statistical analysis

The analyzed data was retrospectively collected from our internal 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. LTC, OS, and PFS were evaluated employing 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.

Results

Median diameter of the target lesion was 2.2 cm (range, 1.0-8.6 cm) treated with a median D_{100} of 14.9 Gy (range, 4.5-20.6 Gy). All 47 LNM were located in the retroperitoneal space at/below the coeliac trunk and superior to the aortic bifurcation in a paraaortic, paracaval, or interaortocaval distribution. In case of irradiation in the vicinity of an OAR, the intended minimum tumor dose (D_{100}) had to be lowered; therefore, eight out of 47 lesions received less than 10 Gy. During the treatment, no OAR was irradiated in excess of the critical value. Twenty-one patients were treated in one session, three patients received two sessions due to progressive disease within the follow-up period. We treated a median of 2 rLNM per patient (range, 1-4). A mean of 1.4 catheters (range, 1-4) was employed to achieve full coverage of the target lesion, and the mean irradiation time per CTV was 19.6 min (range, 4.1-55.3 min).

Mean hospital stay was 4.7 days (range, 2-12 days). We report two cases of small pneumothoraces that regressed spontaneously (classified as severe adverse event grade 1). We report four other cases of mild or moderate adverse events: one mild allergic reaction (urticaria, itching) to metamizole that was administered post-interventional, it was treated successfully with dimetindene and cimetidine; two other patients had slight side effects like sickness and emesis, and a fourth patient showed asymptomatic hematuria that regressed spontaneously. In one patient with metastasized pancreatic ductal adenocarcinoma, a small post-interventional abscess with a concomitant spondylodiscitis occurred, initially requiring intra-

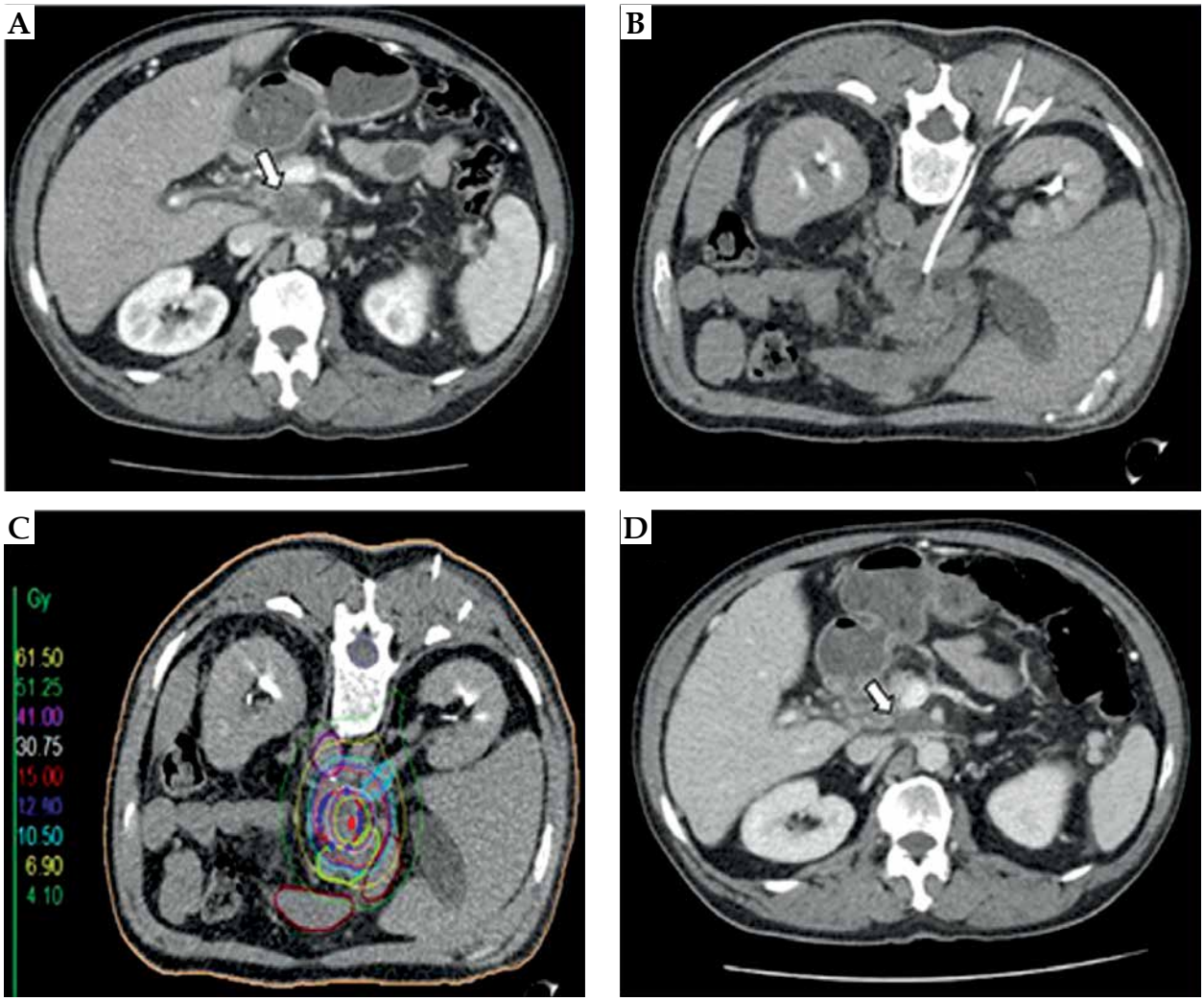

Fig. 1. Interventional technique and local tumor control in a patient with a retroperitoneal lymph node metastasis (rLNM) from pancreatic ductal adenocarcinoma. **A**) Pre-interventional contrast-enhanced CT slice showing a rLNM (white arrow) located below the coeliac trunk; **B**) Peri-interventional CT slice with one percutaneously implanted brachytherapy catheter. The patient is placed in the prone position; **C**) Planning CT with indicated clinical target volume (CTV; blue line), isodose lines, and marked organs at risk (e.g. gastric and duodenal structures). The color-coded isodose levels are shown in Gy (scale on the left side of the image); **D**) Contrast-enhanced CT slice three months after high-dose-rate interstitial brachytherapy showing partial remission of the treated lesion

venous antibiotics; although, seven months post-iBT, an operative short segment fixation was indicated to secure stability of the spine (classified as a severe adverse event grade 3).

During the median follow-up time of 9.6 months (range, 2.9-39.0 months), two patients exhibited local recurrence of GTV at eight months and four months after iBT, resulting in LTC rate of 95.7% in the Kaplan-Meier analysis, including lesions treated with less than 10 Gy (Figure 2). The two recurrent lesions were rLNM of colorectal cancer and a carcinoma of unknown primary (CUP), covered with D_{100} of 20.5 Gy and 4.5 Gy at time of treatment, respectively.

Progression-free survival ranged from 1.4-23.7 months, with a median of 4.2 months (Figure 3). Within the follow-up period, all patients showed systemic progressive disease. In the time between iBT and systemic progression, 10/24 patients received specific tumor therapy (i.e. chemo- and immunotherapy, one patient was treated with iBT of the liver). At time of censoring, 14 out of 24 patients (58%) were still alive, resulting in a median OS of 15.9 months (range, 3.8-39.0 months) (Figure 4).

Discussion

Lymph node metastases are often the first site of metastases in a variety of tumors and, therefore, are critical for staging and prognosis [16]. Nevertheless, patients with a disseminated disease are, according to the current standard of care, in general, treated with adjuvant or palliative chemotherapy depending on the primary tumor and the patient's performance status. In several urological malignancies, a surgical approach is of prognostic and therapeutic value, for instance, in testicular cancer

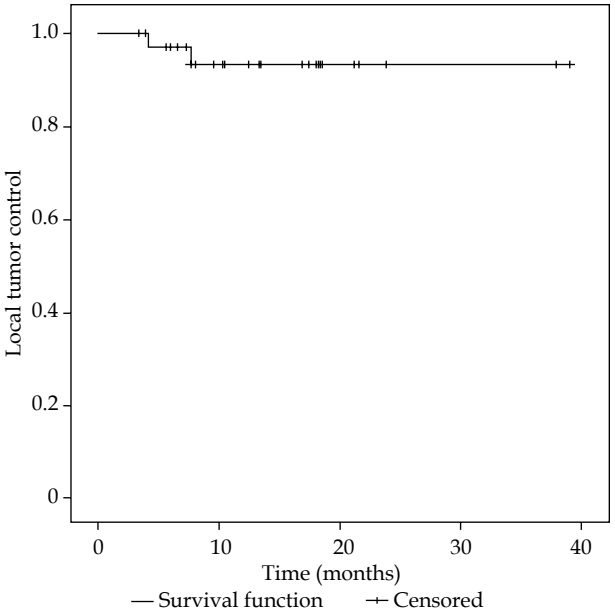

Fig. 2. Local tumor control after high-dose-rate interstitial brachytherapy

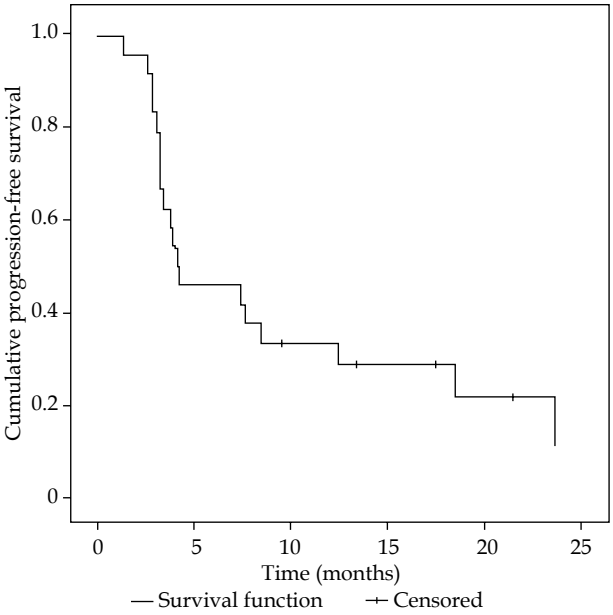

Fig. 3. Progression-free survival after high-dose-rate interstitial brachytherapy

with a reported overall complication rate of 20-35% and mortality of 1% [8,17]. However, retroperitoneal lymph node dissection (RLND) remains controversial for other malignancies, for example in renal cell cancer, a randomized trial failed to show a survival advantage of a complete RLND in combination with a radical nephrectomy compared to radical nephrectomy alone [18]. Nevertheless, in numerous cases, resection might not be possible due to location or accessibility of the metastases, or due to contraindications for surgery or general anesthesia, apart from associated morbidity and mortality.

Data regarding stereotactic body radiotherapy (SBRT) of rLNM are scarce. Bignardi *et al*. treated 19 patients with rLNM of various tumors with SBRT resulting in LTC of 77.8% ±13.9% (median ± standard error) at both 12 and 24 months [19]. In one patient, a grade 3 adverse event occurred, but unclear whether associated with previous surgery or previous conformal radiotherapy. Nonetheless, according to the literature, acute and late toxicities after SBRT of intraperitoneal LNM vary between 14.1-34.0% and 0-11.6% ,with two grade 3 acute and one grade 4 late toxicity events reported in two studies [20,21]. Therefore, the question may arise: what is the benefit of iBT opposed to SBRT? SBRT permits precise but repeated irradiation. The delivery of an effective dose to the target is closely associated with significant exposure of surrounding tissue, resulting in restrictions with respect to size and number of lesions as well as location and, therefore, resulting in varying acute and late toxicities, e.g. for abdominal SBRT [22]. iBT allows one-time radiation with a high ablative dose inside the target volume preserving adjacent OAR from potentially harmful exposure as a result of favorable dosimetric characteristics. Thus, iBT demonstrates opportunities for the radiation of tumors in complex locations without concrete size limitations.

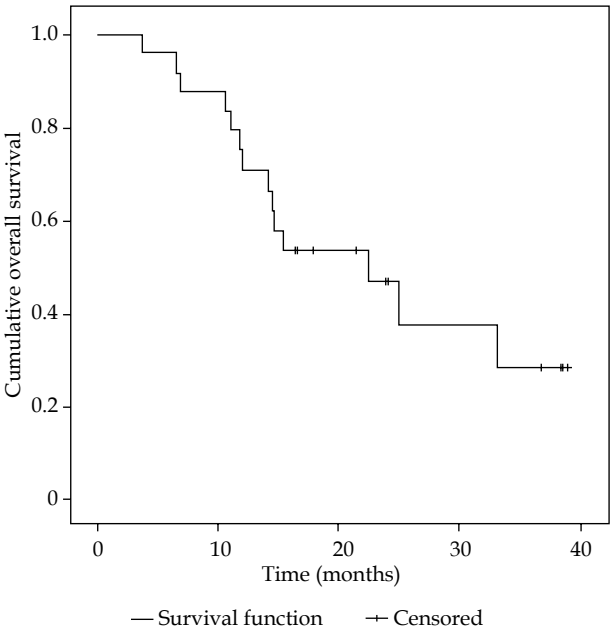

Fig. 4. Overall survival after high-dose-rate interstitial brachytherapy. At date of censoring, 14 out of 24 patients are still alive

Furthermore, in order to enable the delivery of an effective dose in some cases, fiducial markers need to be implanted in or near the tumor before SBRT [23]. Therefore, SBRT can also be an invasive method associated with potential complications such as bleeding, especially if not performed by experienced radiation oncologists.

The applied ablative dose delivered via iBT and SBRT cannot be compared exactly. Recalculation using the linear-quadratic model identifies the equivalent biologically effective dose (eqBED), however, it represents an

approximation. Although the eqBED appears lower for iBT inside the tumor, it theoretically increases exponentially towards the center and would be infinitely high at the point source; additional aspect to consider is the biological effects of one-time radiation compared to repeated radiotherapy [24]. Moreover, our results confirm that the applied dose was sufficient to achieve high local control rate.

Finally, further investigations need to be conducted to enlighten the differences and similarities of the two techniques and especially, to allow appropriate patient selection for both techniques according to the expected outcome.

To our knowledge, apart from case reports and case series [25,26,27], little data exists on the efficacy and safety of percutaneous local ablative techniques including iBT, RFA, and microwave ablation in the treatment of rLNM. There are three studies investigating the feasibility of RFA in the ablation of rLNM. Machi *et al*. performed sonographic-guided RFA in seven patients (colorectal, renal, and prostate cancers), with LTC rate of 71.4% and severe complications such as enterovesical fistula and fecal incontinence [28]. In the study of Arellano *et al*., eight patients with gynecologic malignancies were enrolled, of which only five received treatment (two patients could not be treated due to proximity of adjacent heat-sensitive structures) and did not show any local recurrence or severe adverse events [29]. Gao *et al*. treated 19 patients with retroperitoneal metastasized hepatocellular carcinoma using CT-guided RFA, resulting in LTC rate after 10 months of 41.7% and OS after 1 year of 26.3%, compared to a matched control group with 13 patients and a one-year OS of 7.7% [30]. These findings emphasize the well-known technical limitations of this thermal technique, leading to a potential incomplete ablation and reduced LTC rates, i.e. a large tumor mass (maximal tumor diameter of 5 cm) and major vessels close to the target volume inducing a potential cooling effect. Furthermore, severe adverse events can occur due to the vicinity to critical heat-sensitive organs, requiring a careful patient selection. In contrast, IBT is unrestricted of these limitations and furthermore, compared to surgical resection, offers not only advantages in terms of treatment tolerability but also accessibility of lesions (in number and location).

To our knowledge, no data regarding iBT of rLNM exists; however, Collettini *et al*. treated 10 patients with various tumors and one intraperitoneal LNM with iBT, and reported LTC rate of 80% during median follow-up of 13.2 months [31].

Our study provides superior LTC rate of 95.7% within median follow-up period of 9.6 months. Furthermore, in 24 patients and 47 lesions, we report one severe adverse event grade 3. Although in this patient, an operative intervention was indicated, it should be emphasized that at the day of censoring, the patient is still alive and free of local recurrence or systemic progression after being diagnosed with metastasized pancreatic ductal adenocarcinoma in 2013.

Our findings of median PFS of 4.2 months (range, 1.4-23.7 months) and median OS of 15.9 months (range, 3.8-39.0 months) after iBT are not beneficial from an oncological perspective due to the heterogeneity and rather small cohort; therefore, these results are not comparable to the existing literature. However, at date of censoring, 14 out of 24 patients are still alive; moreover, we report two long-term survivors with 38.5 and 39.0 months after iBT diagnosed with renal cell carcinoma and a malignant pheochromocytoma, respectively.

In general, treatment of metastatic disease is challenging with an increasing tendency towards an individually tailored anticancer therapy to achieve the best possible outcomes. From an oncological perspective, the state of oligometastatic disease has been increasingly spotlighted in treatment strategies of metastatic disease, with the focus on colorectal cancer [32,33]. Therefore, one can argue that in an oligometastatic setting, the rationale for treating rLNM should be the same as for selected patients with liver or lung metastases, with the aim of complete ablation and therefore, the maximal possible reduction of the tumor cell biomass (i.e. cytoreduction) within the bounds of tolerable toxicity. Hence, a rational approach proposes that metastatic ablation can extend PFS, prolong pause of cytostatic treatment, or enable de-escalation to a maintenance therapy. Additionally, considering reported long-term survivors after local ablation or results of studies (e.g. Pan *et al*.) showing a favorable impact of local ablation of LNM of hepatocellular carcinoma on survival (RFA group compared to a non-RFA matched cohort showing median OS of 13.0 months vs. 7.9 months, respectively), confirms that the effect of local ablative techniques on survival is far from being answered [34].

Another important rationale for treating rLNM in rather palliative setting might be the precise ablation of metastases causing symptoms or the ablation of metastases at risk to cause complications in future, in order to decrease clinical symptoms by the reduction of tumor volume or to delay the time to clinical symptoms and therefore, improve the quality of life.

Severe limitations of our study need to be addressed including its retrospective nature and low number of cases. Also, the heterogeneity of the treated cohort with respect to primary tumor, disease stage, and previous treatment resulting in a cumulative PFS and OS that is not beneficial from an oncological perspective. Therefore, a prospective trial with a higher caseload limited to a distinct tumor entity might enlighten the oncological effect of iBT with respect to the primary tumor and the disease stage.

In spite of these limitations, our study demonstrates that iBT is not only a feasible alternative to SBRT or RLND with treatment and primary tumor independent effective LTC rates, but also offers a well-tolerated and safe therapeutic option in the multidisciplinary management of oligometastatic selected patients.

Conclusions

For patients presented with oligometastatic rLNM, iBT is a safe and particularly effective ablative technique that provides a promising treatment option.

Disclosure

Authors report no conflict of interest.

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