Aus der Klinik für Radiologie und Nuklearmedizin
der Medizinischen Fakultät
der Otto-von-Guericke-Universität Magdeburg

Evaluierung der Effektivität der bildgeführten, interstitiellen HDR-Brachytherapie in der Behandlung gastrointestinaler, hepatisch und peritoneal metastasierter Tumorentitäten.

Dissertation

zur Erlangung des Doktorgrades
Dr. med.
(doctor medicinae)

an der Medizinischen Fakultät
der Otto-von-Guericke-Universität Magdeburg

vorgelegt von Ralph Drewes
aus Paderborn
Magdeburg 2019

Angefertigt von April 2018 bis November 2019 in der Klinik für Radiologie und Nuklearmedizin.

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Bibliographische Beschreibung:

Drewes, Ralph:

Evaluierung der Effektivität der bildgeführten, interstitiellen HDR-Brachytherapie in der Behandlung gastrointestinaler, hepatisch und peritoneal metastasierter Tumorentitäten. 2019 – 59 BL

Kurzreferat:

Die herausfordernde, onkologische, multimodale Therapie von Patienten mit metastasierten Tumorerkrankungen erfordert eine zunehmend interdisziplinäre Expertise. Die inhärente Prognoserelevanz von Fernmetastasen begründet je nach Tumorentität den Bedarf und die Applikation von lokalen Therapieverfahren variabler Radikalität.

Die bildgeführte, interstitielle Hochdosis-Brachytherapie (iBT) als Vertreter der lokalen Ablationen wird komplementär zur Chemotherapie und mit der Intention der lokalen Tumorkontrolle, zur Zytoreduktion, sowie der Verlängerung des Überlebens eingesetzt.

Lokale Ablationen wie die iBT offerieren den Patienten eine weniger invasive Therapieoption als das bei manchen Tumorentitäten teilweise als „Goldstandard“ etablierte lokale Therapieverfahren der chirurgischen Resektion.

Die vorliegende Arbeit beschäftigt sich mit der Effektivität der iBT bei der Behandlung von Metastasen duktaler Adenokarzinome des Pankreas, Adenokarzinom des Magens sowie von Gastrointestinalen Stroma-Tumoren. Die Patienten aus den jeweiligen Studienkollektiven waren vor iBT progredient unter Systemtherapie oder unter „Chemopause“. Die iBT kam daher als Salvage Therapie zum Einsatz. Die behandelten Metastasen waren überwiegend hepatisch, jedoch auch peritoneal und vereinzelt an anderen Lokalisationen und wurden als chirurgisch unresektabel eingestuft oder die Resektion vom Patienten abgelehnt.

Die Ergebnisse der drei retrospektiven, einarmigen Studien suggerieren einen Überlebensvorteil für die Patienten durch die Anwendung der iBT bei den untersuchten Tumorentitäten.

Schlüsselwörter: *Brachytherapie, gastrointestinale Stroma-Tumoren, duktales Adenokarzinom des Pankreas, Adenokarzinom des Magens*

Die vorliegende, kumulative Doktorarbeit basiert auf den folgenden aufgeführten Publikationen:

1) **Drewes R**, Omari J, Manig M, Seidensticker M, Hass P, Ricke J, Powerski M, Pech M:
   Treatment of hepatic pancreatic ductaladenocarcinoma metastases with high-dose-rate image-guided interstitial brachytherapy: a single center experience. J Contemp Brachytherapy 2019; 11, 4. 1 - 8

2) Omari J, **Drewes R**, Othmer M, Hass P, Pech M, Powerski M:
   Treatment of metastatic gastric adenocarcinoma with image guided high-dose-rate, interstitial brachytherapy as second line or salvage therapy. Diagn Interv Radiol. 2019 Jul 26.

3) Omari J, **Drewes R**, Matthias M, Mohnike K, Seidensticker M, Seidensticker R, Streitparth T, Ricke J, Powerski M, Pech M:
   Treatment of metastatic, imatinib refractory, gastrointestinal stroma tumor with image-guided high-dose-rate interstitial brachytherapy. Brachytherapy. 2019 Jan - Feb;18(1):63-70.

Die veröffentlichten Publikationen sind in der Dissertation (unter 6.) aufgeführt.

Inhaltsverzeichnis

Abkürzungen:

%	Prozent
BDA	Biliodigestive Anastomose
Ci	Curie
CRC	Colorectal Carcinoma
CT	Computertomographie
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
ECOG PS	Eastern Co-operative Oncology Group Performance Status
ESMO	European Society for Medical Oncology
Gd-EOB-DTPA	hepatozytenspezifisches MR-Kontrastmittel (Primovist)
GIST	gastrointestinaler Stromatumor
Gy	Gray
HCC	hepatocellular carcinoma
iBT	bildgeführte, interstitielle Hochdosis-Brachytherapie
LITT	Laser induzierte Thermotherapie
MRT	Magnetresonanztomographie
MWA	Mikrowellenablation
NCCN	National Comprehensive Cancer Network
OAR	Organs at Risk
PDAC	pancreatic ductal adenocarcinoma
PPPD	Pylorus-erhaltende partielle Pankreatiko Duodenektomie
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequenzablation
SBRT	Stereotactic Body Radiation Therapy
TKI	Tyrosinkinase Inhibitor

1. Einführung

Minimal invasive, lokal ablative Verfahren gewinnen durch weitreichende Behandlungserfolge in den letzten Jahren stetig an Popularität und Relevanz. Aufgrund der zunehmenden Interdisziplinarität eines jeden onkologischen Therapiekonzeptes zur Behandlung von Tumorerkrankungen im (oligo-) metastatischen Stadium, können den Patienten mannigfaltige Optionen variabler Radikalität bzw. Invasivität in Abhängigkeit vom Patientenwusch, Komorbiditäten und der lokalen Expertise offeriert werden.

Minimal invasive Therapieverfahren besitzen infolge dessen einen wichtigen Stellenwert neben den traditionellen drei Säulen der Onkologie – Chirurgie, Strahlentherapie und Systemtherapie (Chemo- und Immuntherapie). Lokale Ablationen eröffnen vielfach neue Therapiemöglichkeiten im komplementären oder sogar alternativen Einsatz sowohl zur systemischen Chemotherapie als auch zur chirurgischen Resektion.

Fernmetastasen stellen trotz des wachsenden Arsenals an antineoplastischen Therapieoptionen für jedes onkologische Behandlungskonzept weiterhin eine große Herausforderung dar und haben zugleich eine inhärente prognostische Relevanz und therapeutische Konsequenz.

Ziele einer interventionell-radiologischen Lokalablation oder operativer Verfahren im palliativen Setting bzw. metastasierten Stadium sind daher die zumindest temporäre lokale Tumorkontrolle, Tumordebulking und eine Verzögerung einer Tumorprogression. Patienten mit einer oligometastatischen Tumorerkrankung erreichen je nach Entität selten eine komplette Remission. Gesondert hervorzuheben sind die Daten der CLOCC Studie (siehe 1.1), welche bei metastasierten CRC Patienten im kombinierten Therapiearm (Resektion+RFA) nach einem Follow-Up von knapp 10 Jahren ein „Langzeitüberleben“ von 35% demonstriert [1]. Ergebnisse aus Studien mit kleinen Patientenkollektiven suggerieren ebenfalls einen Überlebensvorteil durch lokale Therapieverfahren [2,3]. Diese „Indizien“ müssen jedoch teilweise noch durch prospektive, randomisierte Studien mit größeren Fallzahlen (RCT Phase II und III) validiert werden, um das Indikationsspektrum lokaler Ablationen zu erweitern.

Bei primär resektablen Tumorerkrankungen im frühen Stadium fungiert die chirurgische Herangehensweise in der Regel als Erstlinientherapie mit kurativer Intention. Für Patienten mit fortgeschrittener bzw. metastasierter oder unresektabler Tumorerkrankung stellt die – oft palliative - Therapie weiterhin eine je nach Tumorentität schier unlösbar erscheinende Aufgabe dar. Restriktionen oder Kontraindikationen eines chirurgischen Ansatzes sind ein reduzierter Allgemeinzustand bzw. Performance Status (ECOG PS), Komorbiditäten, unzureichende zu erwartende Organfunktion (nach Resektion), eine absehbare R2 Resektion sowie eine fehlende Einwilligung der Patienten zum offen chirurgischen Verfahren. Als Organ mit den häufigsten Fernmetasten wird die Leber dementsprechend oft Gegenstand lokal therapeutischer Erwägungen, da Lebermetastasen außerdem in aller Regel ein entscheidender prognoserelevanter Faktor sind. Nach objektiver und leidenschaftsloser Evaluation aller individuellen Faktoren, sind zum Zeitpunkt der Diagnosestellung bei strikter Indikationsstellung tatsächlich nur die wenigsten aller Lebertumoren, je nach Entität ca. 10-20%, operabel bzw. eine Resektion indiziert [4]. In einigen Fällen gelingt ein „down-staging“ von potenziell resektablen Metastasen in Anzahl oder Größe durch Radiochemo- oder Immuntherapie wodurch dann schließlich die Indikation zur lokalen Therapie doch noch gerechtfertigt werden kann bzw. rational erscheint.

Aufgrund der Vielzahl inoperabler Tumoren bzw. Metastasen und der damit limitierten Therapieoptionen wuchs der Bedarf an Alternativen, was die Entwicklung diverser minimal-invasiver Therapien und deren Applikation im klinischen Alltag vorantrieb. Wie bei chirurgischen Verfahren ist auch bei minimal invasiven Verfahren eine adäquate Patientenselektion die Voraussetzung für einen Therapieerfolg. Bei ausgewählten Patienten repräsentieren lokale Ablationsverfahren eine ebenbürtige Alternative mit vergleichbarer Radikalität wie chirurgische Verfahren, sind zudem kosteneffizienter und oftmals schonender für gesundes Parenchym und Patient [5].

Die Rationale einer extensiv lokal durchgeführten Therapie und der daraus erhoffte Überlebensvorteil werden jedoch bisweilen je nach Tumorentität auch kontrovers diskutiert. Für einige Entitäten (hepatozelluläres Karzinom, kolorektales Karzinom) wurde bereits Evidenz durch klinische Studien hergestellt und dementsprechend auch Empfehlungen in einschlägigen internationalen Leitlinien verankert [6,7].

1.1. Übersicht lokal ablativer Therapieverfahren

Die populärsten lokalen Therapieoptionen und deren Anwenderbarkeit sollen im Folgenden kurz Erwähnung finden, um einen Vergleich zur Ablationsmethode der vorliegenden Arbeit (Brachytherapie) herstellen zu können.

Frühe minimal invasive, chemische Verfahren wie die intratumorale Ethanol- oder Essigsäureinjektionen sind mittlerweile weitgehend obsolet und durch thermische Ablationen ersetzt worden.

Die ersten Vertreter thermaler Ablationsverfahren, die Radiofrequenzablation (RFA) und die Laserablation (Laser induzierte Thermotherapie – LITT), kommen als Alternative zur Resektion seit Anfang der 1990er Jahre zum Einsatz [8,9]. Seither wurde das Sortiment der thermalen Ablationen ergänzt durch die Mikrowellenablation (MWA) und Kryoablation [10–12]. Die populärste thermale Ablationsmethode ist bis heute die RFA, die mittlerweile an vielen Tumorzentren als Standardverfahren etabliert ist [13].

Die Studienlage zum Outcome bzw. der klinische Nutzen der RFA variiert je nach Tumorentität. Die Validierung der Methodik ist derzeit beim hepatozellulären Karzinom (HCC) sowie beim kolorektalen Karzinom (CRC) am weitesten fortgeschritten.

Die Gleichrangigkeit der RFA zur Resektion bezüglich Gesamtüberleben und tumorfreier Überlebenszeit wurde erstmals 2006 von Chen et al. zur Therapie des hepatozellulären Karzinoms (HCC) in einer prospektiven Studie etabliert [14]. Retrospektive Studien suggerieren sogar die Überlegenheit der perkutanen RFA gegenüber einer chirurgischen Resektion bei HCCs bis zu einem Durchmesser von 2 cm [15].

Ähnliche Erfolge der RFA konnten auch in der Therapie von Lebermetastasen des CRC verzeichnet werden. Ruers et al. demonstrierten in einer randomisierten Studie (RCT) zur RFA bei unresektablen CRC Lebermetastasen ein signifikant verlängertes progressionsfreies Überleben (16,8 vs. 9,9 Monate) bei Applikation von RFA in Kombination mit Chemotherapie als die Chemotherapie allein [16].

Die Ergebnisse der Phase II CLOCC Studie (Chemotherapy and local ablation versus Chemotherapy) belegen einen signifikanten (Langzeit-) Überlebensvorteil bei

Anwendung einer aggressiven Lokaltherapie (RFA+Resektion) in Kombination mit Chemotherapie im direkten Vergleich zur alleinigen Chemotherapie in der Behandlung von unresektablen CRC Lebermetastasen [1,17].

Eine Phase III Studie (COLLISION Trial - Colorectal Liver Metastases: Surgery vs Thermal Ablation, a Phase III Prospective Randomized Controlled Trial) soll die thermale Ablation (RFA und MWA) mit der chirurgischen Resektion von CRC Lebermetastasen (<3 cm) vergleichen – Ergebnisse werden 2022 erwartet.

Die Datenlage aus diversen Studien zu thermalen Ablationsverfahren, insbesondere der RFA, offenbart jedoch bei allen Erfolgen auch einige Limitationen der Methodik. Die rational therapierbare Tumorgröße hat ein oberes Limit von 3-4 cm Durchmesser, inklusive Sicherheitssaum insgesamt 5 cm [18]. Nähe zu thermosensiblen Risikostrukturen wie intrahepatischen Gallenwegen oder auch hohe Tumorvaskularisation führen zu reduzierter Effektivität thermaler Ablationsverfahren aufgrund vaskulärer Wärmeableitung bzw. Kühlungseffekte, genannt „Heat-Sink-Effect“ [19]. Diese Einflussfaktoren haben unmittelbare, negative Implikationen auf die lokale Kontrolle der therapierten Läsionen. Hilusnahe oder subkapsuläre Lebertumoren sind aufgrund der beschriebenen Restriktionen nur sehr eingeschränkt durch thermale Ablationsverfahren therapierbar.

Die Limitationen thermaler Verfahren waren und sind ein wesentlicher Anreiz zur Entwicklung einer alternativen, lokalen Therapiemethode, welche diese Restriktionen zu überwinden vermag und damit neue Möglichkeiten eröffnet.

Eine Methode, welche nicht zu der Kategorie der thermalen Ablationsverfahren gehört, ist die interstitielle Hochdosis-Brachytherapie, welche die lokale Ablation bzw, DNA Schäden unterschiedlichen Ausmaßes mit konsekutiver Tumorzelleradikation durch Hochdosis Bestrahlung induziert. Das Verfahren wird im folgenden Unterkapitel detailliert beschrieben.

1.2. Bildgeführte, interstitielle Hochdosis (HDR)-Brachytherapie

Die Brachytherapie arbeitet mit umschlossenen Strahlungsquellen, die intra- oder peritumoral platziert werden. Die ersten interstitiellen Brachytherapie Applikationen als onkologisches Therapieverfahren wurden mit Radium Nadeln durchgeführt und boten nur minimalen Strahlenschutz für die behandelnden Ärzte. Modernere Techniken benutzen ein ^{192}Iridium Radionuklid als Strahlenquelle über eine Computergesteuerte „Afterloading" Technik, eingeführt durch Henschke et al. (1964). Dadurch wurde die Problematik der Strahlenexposition des applizierenden Personals gelöst. Die Weiterentwicklung der Technik ermöglichte eine breitere Anwendbarkeit der Brachytherapie.

Die ersten Prozeduren einer CT gestützten Brachytherapie sowie die Benutzung eines Software-Systems (ursprünglich für Brachytherapie bei Cervix-Ca entwickelt) zur Planung und Therapie wurden von Zamboglou et al. Ende der 90er Jahre sowie Ricke et al. Anfang der 2000er Jahre durchgeführt. [20,21] Die CT gestützte, interstitielle Brachytherapie kombiniert die ^{192} Iridium Brachytherapie mit moderner CT Bildkontrolle sowie 3D Planung und Dosimetrie. Seit der klinischen Einführung wird die Prozedur thorako-abdominell bzw. intra- und extrahepatisch eingesetzt und es bestehen nur wenige Limitationen bezüglich der zu therapierenden Tumorentität oder Lokalisation [22,23]. Das Verfahren der perkutanen, bildgeführten, interstitiellen Hochdosis Brachytherapie (iBT) ermöglicht eine exakte Positionierung der Afterloading Katheter und infolge dessen eine optimale dreidimensionale Bestrahlungsplanung anhand von 3D Schnittbild-Datensätzen [24]. Je exakter die intratumorale Platzierung der Strahlenquelle, desto zielgenauer und mit höherer Strahlendosis kann das klinische Zielvolumen (clinical target volume - CTV) bei gleichzeitiger Schonung der sensiblen Organe und Strukturen (Organs at Risk - OAR) bestrahlt werden. Zum Tumorzentrum steigt die Dosis exponentiell weit jenseits von 50 Gy, während sie in der Peripherie stark abfällt und gesundes Gewebe so bestmöglich ausgespart wird [24].

Komplikationen Grad III CTCAE (Common Terminology Criteria for Adverse Events) im Rahmen einer iBT werden in der Literatur mit einer Häufigkeit von < 3% beziffert [25]. Kollateralschäden anderer Organe und Blutungen sind in der Regel durch die bildgeführte Insertion der Strahlenquelle selten. Bei ungünstiger Tumor- und oder Katheterlage kann es zu ungeplanten strahlungsbedingten Komplikationen kommen

– am häufigsten sind hiervon Teile des Gastrointestinaltraktes betroffen. Die OARs werden daher im Rahmen der Bestrahlungsplanung vom interventionellen Radiologen, der die Katheter platziert hat, eingezeichnet. Die mukosale gastrische Toleranzdosis wurde von Streitparth et al. 2006 untersucht: die Grenzdosis für gastrische Toxizität liegt bei einer D_{1ml} von 11 Gy und für gastrische bzw. duodenale Ulzerationen bei 15,5 Gy [26].

Erfahren OARs wie der GI-Trakt im Rahmen einer iBT eine kritische Dosisexposition oberhalb der Grenzwerte, so ist in jedem Fall eine mindestens sechswöchige Prophylaxe mit Protonenpumpeninhibitoren indiziert. Werden Tumoren nahe des biliären Systems im Falle einer Gallenwegsdilatation oder klinischen/laborchemischen Cholestase therapiert, so wird im Einzelfall eine empirisch basierte Entscheidung zur antibiotischen Abschirmung getroffen.

Im Rahmen eines extensiven Tumorzerfalls (Tumorlyse-Syndrom) bei Bestrahlung großer Volumina kann es vorübergehend zu einer postinterventionellen Inflammationsreaktion mit Liberation von Entzündungsmediatoren und Zytokinen kommen, welche bis zu 6 Stunden nach der Behandlung eine unspezifische Fiebersymptomatik zur Folge haben kann. Dieser Symptomatik kann jedoch medikamentös entgegengewirkt werden. Zur Regulation des Harnsäurespiegels kann prophylaktisch Allopurinol oder therapeutisch Rasburicase gegeben werden.

1.3. Patientenselektion

Wie eingangs erwähnt ist die Patientenselektion der erste Schritt bzw. die Basis des Therapieerfolges. Die Indikationsstellung zur iBT als Baustein einer multimodalen Therapie erfolgt in domo in der Regel im Rahmen eines interdisziplinären, gastrointestinalen Tumorboards, welches von Radiologen, Viszeralchirurgen, Gastroenterologen, Onkologen, Pathologen, und Strahlentherapeuten besetzt wird. In Einzelfällen wird die Indikation zur iBT nach Vorstellung der Patienten über externe Zuweiser in der radiologischen Ambulanz für Mikrotherapie gestellt. Im Tumorboard wird primär die Möglichkeit einer potentiell kurativen Resektion ausgelotet. Im Anschluss werden verschiedene Therapiemöglichkeiten diskutiert. Minimal invasive, lokale Ablationen bieten in vielen Fällen eine direkte Alternative zur offenen Chirurgie als Erstlinientherapie, können jedoch auch als Zweit-, Dritt- oder Viertlinientherapie bzw. als Salvage Therapie eingesetzt werden.

Einschlusskriterien für die iBT sind: (1) adäquate Koagulationsparameter (Thrombozyten > 50,000/nl, PTZ/Quick > 50%, partielle Thromboplastinzeit (PTT) <50s), (2) Leberfunktionsstatus in Child-Pugh Klasse A oder B, (3) Gesamt-Bilirubin <2 mg/dl, (4) ECOG 0-2, in Ausnahmefällen ECOG 3, (5) oligometastatische (≤ 5 Metastasen) Tumorerkrankung, (6) Patienteneinwilligung.

Ausschlusskriterien einer iBT sind: (1) disseminiertes Tumorleiden, (2) Nachweis eines progressiven Tumorstadiums mit „aggressiver" Biologie, (3) fehlende Patienteneinwilligung/-Bereitschaft. Ein oberer Grenzwert bezüglich des maximal therapierbaren Tumordurchmessers existiert in domo nicht; sofern notwendig wird eine mehrzeitige iBT durchgeführt.

Bei Laborwerten außerhalb der Toleranz, beispielsweise der Hämostase, in der präinterventionellen Blutbildkontrolle, kann dementsprechend mit Transfusionen reagiert werden. Aszites kann präinterventionell drainiert werden, um den Zugang zu erleichtern und das Blutungsrisiko zu minimieren.

1.4. Interventionelle Technik und Bestrahlungsplanung

Die zur iBT an unserer Klinik stationär aufgenommenen Patienten bekommen präinterventionell eine aktuelle Bildgebung mittels eines MRT der Leber bzw. des Oberbauches nach Applikation eines Hepatozyten spezifischen Kontrastmittels, Gb-EOB-DTPA (Primovist, Bayer Pharma, Leverkusen, Deutschland). Je nach Tumorentität und Lokalisation werden alternativ oder zusätzlich ein MRT des Abdomens und ein CT des Thorax und Abdomens mit jodhaltigem Kontrastmittel akquiriert. Zweck dieser aktuellen Bildgebung sind die Planung der technischen Durchführung der iBT, die Taxierung des zu behandelnden Tumorvolumens und ein aktuelles Staging zur Beurteilung eines etwaigen Tumorprogresses. Im Falle eines ausgedehnten Tumorprogresses muss ggf. die Lokaltherapie mittels iBT ausgesetzt und ein alternatives Therapiekonzept aufgestellt werden.

Der strukturierte Ablauf einer iBT verläuft in folgenden Schritten:

1. Interventionsbesprechung
2. Patientenvorbereitung und Management
3. Implantation der Afterloadingkatheter unter CT-/MRT Fluoroskopie

4. Dreidimensionale Bestrahlungsplanung
5. Hochdosis Bestrahlung in Afterloading Technik
6. Katheterentfernung und Monitoring

Vor Beginn der Intervention bekommt der Patient eine Infusion mit jeweils 8 mg Fortecortin und Zofran zur prophylaktischen Antiemese sowie zur Vermeidung akuter Strahlenfolgen wie hepatische VOD (Lebervenen-Verschlusskrankheit) und Ödem. Unmittelbar bei Beginn und während der iBT werden Analgesie (Fentanyl), Sedation (Midazolam) und Lokalanästhesie (Lidocain) gewichtsadaptiert und je nach Bedarf bzw. Schmerzempfinden des Patienten appliziert. Mit einer 18-G Hohlnadel wird unter CT-/MR-Fluoroskopie (Toshiba/Canon, Aquilion, Japan; Panorama 1.0T, offenes MR System, Philips Healthcare) der Tumor bzw. die Zielläsion punktiert. In einem nächsten Schritt werden ein steifer Angiographiedraht (Amplatz, Boston Scientific, Marlborough, USA) und schließlich eine flexible 6-French Katheterschleuse (Radifocus, Terumo) in Seldinger Technik in die Zielläsion eingeführt. Als letztes wird der 6-French Afterloading Katheter (Afterloadingkatheter, Primed Medizintechnik Gmbh, Halberstadt, Deutschland) über die Schleuse inseriert und das Katheterende mittels kutaner Naht und sterilen Bandagen vorübergehend fixiert. Die Größe des CTV und die OARs bestimmen die Anzahl der implantierten Katheter und deren Angulation. Im Anschluss wird ein CT oder MRT mit Kontrastmittel durchgeführt, um die Lage der Katheter zu verifizieren, etwaige Blutungskomplikationen auszuschließen und die Bestrahlung zu planen. Der interventionelle Radiologe und der Strahlentherapeut markieren das CTV und die OARs in jeder CT oder MRT Schicht.

Das Bestrahlungsdesign wird mit dem akquirierten Datensatz und dem Software System Oncentra (Nucletron, Elekta Ab, Stockholm, Schweden) geplant. Die Software ist integraler Bestandteil des Hochdosis Afterloading Systems. Die dreidimensionalen Koordinaten (x, y, z) der Spitze jedes implantierten Katheters sowie des Verlaufs in Relation zur Tumorgrenze werden in der Planungssystem transferiert. Die kalkulierten Isodosis Linien werden in jeder Schicht kontrolliert und an das CTV angepasst.

Das Afterloading bzw. iBT System (Nucletron, Elekta Ab, Stockholm, Schweden) arbeitet mit einer ^{192}Iridium Strahlungsquelle mit einer nominalen Aktivität von 10 Ci (370GBq). Die Bestrahlung im Rahmen einer iBT erfolgt als Hochdosis Einzelfraktion.

Die verschriebene Minimaldosis zur Abdeckung des gesamten CTV variiert je nach Tumorentität zwischen 12 und 25 Gy. Im Tumorzentrum findet eine exponentielle Steigerung der Bestrahlungsdosis auf > 50 Gy statt. Die von der Tumorentität abhängige Minimaldosis wurde in verschiedenen Studien ermittelt. Die Grenzen zu den OARs und deren Toleranzdosen werden bei der Bestrahlung entsprechend berücksichtigt. Die Bestrahlungsdauer beträgt in der Regel zwischen 20 und 40 Minuten und ist abhängig vom CTV und von der Stärke der Strahlenquelle, welche stetig abnimmt und daher nach einigen Monaten im Zuge einer Gerätewartung in der Strahlentherapie ausgetauscht werden muss.

Nach Abschluss der Bestrahlung werden die Angiographieschleusen inklusive der Bestrahlungskatheter entfernt und die Stichkanäle mit resorbierbarem, thrombogenem Material (Gelfoam, Pfizer Inc, New York, New York) versiegelt, um Nachblutungen zu vermeiden.

1.5. Therapieansprechen / Follow-Up

Die erste Therapiekontrolle der iBT erfolgt in der Regel nach einem Intervall von 6 – 12 Wochen je nach Tumorentität und Lokalisation mittels eines Leber MRTs und eines CT des Thorax und Abdomens jeweils mit Kontrastmittel. Klinischer Status und Laborchemie werden ebenfalls routinemäßig erhoben. Nach durchgeführter iBT ist im Leber MRT in der hepatobiliären Spätphase 20 Minuten nach Gd-EOB-DTPA Applikation ein hypointenser Randsaum um die Läsion zu beobachten. Dieser korreliert mit dem (teilweise reversiblen) Funktionsverlust der Hepatozyten und entspricht der strahleninduzierten, fehlenden Aufnahme von leberspezifischem Kontrastmittel. Der Schwellenwert für einen Funktionsverlust der Hepatozyten bei Bestrahlung von Lebergewebe wurde mit einer Einzeldosisbestrahlung von 10 Gy beziffert [27]. Lokale Tumorkontrolle nach iBT wurde korrespondierend zu den Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Kategorien stable disease (SD), partial remission (PR) und complete remission (CR) definiert. Eine Größenprogredienz des bestrahlten Tumors oder neu aufgetretenes, knotiges Wachstum im Randbereich des Ablationsareals wird als lokale Tumorprogression eingestuft. Das Auftreten neuer Metastasen und eine Größenprogredienz >20% von

untherapierten Läsionen im Follow-Up wird als systemische Tumorprogredienz deklariert.

1.6. Zielsetzung der Arbeit

Die vorliegende Arbeit basiert auf einer retrospektiven Datenauswertung von iBTs sekundärer Lebermalignome sowie extrahepatischer Tumormanifestationen dreier verschiedener, gastrointestinaler Tumorentitäten. Die Eingriffe wurden an unserer Klinik zwischen August 2009 bis März 2017 durchgeführt. Die Daten der onkologischen Patienten werden in einer klinikeigenen Datenbank (ASENA) digitalisiert und archiviert. Die über diesen Zeitraum gesammelten Daten wurden aus ASENA und MEDICO gebündelt und detailliert retrospektiv ausgewertet.

Ziel der Arbeit und der retrospektiven Analyse war die Beurteilung der Effektivität und Sicherheit der iBT als Baustein eines antineoplastischen Konzeptes einer multimodalen Therapie von unresektablen intra- und extrahepatischen Malignomen.

Im Detail wurde die bildgeführte, interstitielle Hochdosis-Brachytherapie von Metastasen duktaler Adenokarzinome des Pankreas (**Originalarbeit 1**), von Adenokarzinomen des Magens (**Originalarbeit 2**) sowie von GIST (Gastrointestinalen Stromatumoren, **Originalarbeit 3**) untersucht.

2. Eigene Arbeiten

2.1. Treatment of hepatic pancreatic ductaladenocarcinoma metastases with high-dose-rate image-guided interstitial brachytherapy: a single center experience. (Originalarbeit 1)

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

Treatment of hepatic pancreatic ductaladenocarcinoma metastases with high-dose-rate image-guided interstitial brachytherapy: a single center experience. J Contemp Brachytherapy 2019; 11, 4: 1–8

In den einschlägigen, aktuellen Leitlinien (NCCN Clinical Practice Guidelines in Oncology, ESMO European Society for Medical Oncology) existiert über die Systemtherapie hinaus weiterhin kein Konsens zur Therapie des unresektablen, metastasierten Adenokarzinoms des Pankreas. Das mediane Gesamtüberleben des metastasierten, unbehandelten PDAC beläuft sich in Übereinstimmung mehrerer Studien auf einen Zeitraum von sechs Monaten. Neuere Chemotherapie Kombinationen wie FOLFIRINOX und Gemcitabine mit Nab-paclitaxel sind rational betrachtet lediglich Patienten mit ECOG PS 0 oder 1 administrierbar, was im Schnitt auf 15-25% sämtlicher PDAC Patienten zutrifft. Ein ECOG PS von 2 limitiert die Optionen laut Guidelines auf Gemcitabine Monotherapie. Ein potenzieller Benefit einer PDAC Metastasen Chirurgie wurde bislang noch nicht suffizient mittels Studien validiert.

Die Patienten unseres Studienkollektives hatten keine weitere systemische Therapieoption und hatten im letzten Staging vor iBT einen Progress. Eine Gesamtzahl von 45 Metastasen, verteilt auf 16 Patienten, wurde mittels iBT bestrahlt. Das mediane Gesamtüberleben, kalkuliert mit der Kaplan Meier Methode ab dem Zeitpunkt der jeweiligen iBT, beträgt 8,9 Monate – ab dem Zeitpunkt der PDAC Erstdiagnose 27,5 Monate.

Die Ergebnisse dieser retrospektiven Studie mit kleiner Fallzahl suggerieren einen deutlichen Überlebensvorteil durch Applikation einer lokalen Therapie (iBT) als Salvage Manöver bei PDAC Patienten zur Behandlung und Kontrolle der Metastasen bei geringer „CTCAE 3+ Komplikationsrate“ (3 aus 45 iBT Interventionen).

2.2. Treatment of metastatic gastric adenocarcinoma with image guided high-dose-rate, interstitial brachytherapy as second line or salvage therapy. (Originalarbeit 2)

Omari J, **Drewes R**, Othmer M, Hass P, Pech M, Powerski M:

Treatment of metastatic gastric adenocarcinoma with image guided high-dose-rate, interstitial brachytherapy as second line or salvage therapy. Diagn Interv Radiol. 2019 Jul 26.

Das mediane Gesamtüberleben des metastasierten Adenokarzinoms des Magens beläuft sich ohne Therapie auf 3-5 Monate und mit palliativer Chemotherapie auf ca. 11 Monate, bei Zweitlinien Therapie und HER2 Therapie bis zu 13 Monate. Die Therapie stellt eine Herausforderung dar; auch bei dieser Tumorentität gibt es keinen Konsensus bezüglich der weiteren Herangehensweise im metastierten Stadium. Sowohl Gastrektomie als auch Metastasektomie sind im fortgeschrittenen/fernmetastasierten Stadium experimentell und prospektive Daten fehlen, um ein etwaiges aggressiveres Vorgehen zu rechtfertigen bzw. validieren. Die ESMO Leitlinien raten von Metastasenchirurgie ab, weil Daten bezüglich eines Überlebensvorteils fehlen.

In unserer Studie wurde eine kumulierte Anzahl von 36 Magenkarzinom Metastasen mittels iBT behandelt. Die Patienten hatten vor der iBT bereits palliative Chemotherapie erhalten, Erst- und teilweise auch Zweitlinientherapie. Die Indikation zur iBT war Salvage Therapie bzw. Zytoreduktion.

Das mediane Gesamtüberleben nach iBT war 11,4 Monate, vom Zeitpunkt der Erstdiagnose 33,5 Monate. Lediglich ein Patient hatte eine Komplikation CTCAE Grad III – ein Leberabszess, welcher erfolgreich drainiert wurde.

In unserem kleinen Studienkollektiv und der retrospektiven Analyse mit der Kaplan Meier Methode hatten die Patienten einen zusätzlichen Überlebensvorteil nach iBT mit einem nahezu identischen Zeitraum wie mit alleiniger palliativer Chemotherapie von ca. 11 Monaten.

2.3. Treatment of metastatic, imatinib refractory, gastrointestinal stroma tumor with image-guided high-dose-rate interstitial brachytherapy.
(Originalarbeit 3)

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

Treatment of metastatic, imatinib refractory, gastrointestinal stroma tumor with image-guided high-dose-rate interstitial brachytherapy. Brachytherapy. 2019 Jan - Feb;18(1):63-70.

Gastrointestinale Stromatumoren sind seltene Tumoren des GI-Traktes. Die Systemtherapie besteht aus unterschiedlichen Tyrosinkinase-Inhibitoren, die je nach Bedarf, entwickelter Resistenz und Therapielinie (Imatinib, Sunitinib, Regorafenib) variiert werden.

Die ESMO und NCCN Leitlinien differenzieren zwischen „widespread“ und „limited progressive disease“. Bei „limitierter“ Progression bzw. im oligometastatischen Setting wird die Fortführung einer Systemtherapie mit gleichzeitiger Lokaltherapie der Metastasen suggeriert. Als Beispiele werden Resektion, RFA und (Chemo)Embolisation aufgeführt. Die chirurgische Resektion wird jedoch kontrovers beurteilt und die Wichtigkeit vorsichtiger Patientenselektion betont.

Zehn Patienten, jeweils progredient unter systemischer TKI Therapie, wurden mittels Brachytherapie behandelt – insgesamt 40 Metastasen in 40 iBT Sitzungen. In zwei Interventionen kam es zu einer Komplikation CTCAE Grad III: lokal hepatische Hämorrhagie, behandelt mittels Embolisation in der Angiographie, und ein Pneumothorax, welcher entlastet werden konnte.

Das mediane Gesamtüberleben nach iBT liegt bei 37,3 Monaten, vom Zeitpunkt der Erstdiagnose 107 Monate – der derzeitige Status Quo des Überlebens: sechs Patienten verstorben, vier am Leben. Vergleichbare Studien zur GIST Metastasenchirurgie und RFA untermauern die Conclusio unserer Studie: Systemtherapie in Kombination mit Lokaltherapie kann bei selektierten Patienten in einem Überlebensvorteil resultieren.

3. Diskussion

Im metastasierten Stadium stellen Tumorerkrankungen unterschiedlichster Entitäten eine große therapeutische Herausforderung dar. Kurative intendierte Therapiekonzepte sind abhängig von Tumorart und Ausdehnung oft unmöglich. Die Wahrscheinlichkeit eines Langzeitüberlebens wird traditionell als gering eingeschätzt, Ergebnisse aus der eingangs erwähnten CLOCC Studie sind jedoch vielversprechend und demonstrieren nach „aggressiver“ Lokaltherapie (RFA und Resektion) bei metastasierten CRC Patienten ein Überleben von 35% nach knapp 10 Jahren im Gegensatz zu einem Überleben von 10% bei Chemotherapie (ohne lokale Therapie)[1].

Im komplementären Einsatz zur systemischen Chemotherapie sowie als Konkurrenzverfahren zur chirurgischen Resektion etablieren sich zunehmend die lokalen Therapie-/Ablationsverfahren. Die Rationale extensiver Anwendung lokaler Therapieverfahren besteht in der zumindest temporären Tumorkontrolle sowie in der Reduktion des statistischen Risikos bzw. der Wahrscheinlichkeit einer Chemotherapie resistenten, klonalen Selektion (Goldie-Goldman Hypothese, 1970er Jahre). Die lokale Ablation ermöglicht eine Destruktion von klonalen Zellen, welche sich insensitiv gegenüber der jeweiligen, gegenwärtigen Chemotherapie erweisen. Dies suggeriert einen möglicherweise idealen Zeitpunkt für eine lokale Ablation des residualen Tumorvolumens nach Chemotherapie zur Eradikation resistenter, klonaler Zellen. Oligotope Distribution stellt in der Regel das obere Limit für die sinnvolle Anwendung lokaler Ablationen dar; es existiert jedoch kein Konsens zur Definition des Terminus „oligometastatisch“ (z.B. ≤ 5 Metastasen, ≤ 10 Metastasen). In Abhängigkeit vom Tumorvolumen können jedoch darüber hinaus auch zytoreduktive Intentionen in Betracht gezogen werden. Ein weiterer Aspekt für die lokale Therapie ist der metastatische Genotyp, welcher möglicherweise vom Primarius determiniert wird oder aus anderen Metastasen nach Anhäufung einer Kombination aus onkogenen Mutationen resultiert – Letzteres wäre ein weiterer Grund zur Ablation.

Die thermalen Ablationsverfahren unterliegen, wie eingangs bereits erwähnt, einigen Restriktionen in der Anwendbarkeit. Die erzielbare Nekrosezone eines zu koagulierenden Tumors beläuft sich derzeit auf maximal 5 cm Durchmesser. Dies liegt zum einen an der RFA Elektrode und zum anderen an „heat sink effects“

[Goldberg et al. 1998] aufgrund der Tumorvaskularisation oder benachbarter wärmeableitender Gefäße. In Konkordanz dazu konnte in Tiermodellen demonstriert werden, dass um Gefäße mit einem Kaliber ≥ 5 mm in 100% aller Fälle und bei einem vaskulären Kaliber von 3-5 mm in 29% aller Fälle nach thermaler Ablation mittels RFA residuales Tumorgewebe nachweisbar ist [19]. Hepatische Gefäße mit entsprechendem Kaliber sind beispielsweise die Vena Cava, zentrale Pfortaderäste oder die Lebervenen. Das Ausmaß der Gewebenekrose bei der RFA korreliert außerdem direkt mit der Impedanz des Gewebes, welche bis zum Erreichen einer Nekrose und letztlich bis zur Verkohlung stark ansteigt. Es besteht folglich das Risiko einer inkompletten Tumorablation an Grenzflächen unterschiedlicher Gewebe, bei großen Zielvolumina oder bei anatomisch suboptimaler Positionierung der Elektrode.

In verschiedenen Studien wurde zudem herausgearbeitet, dass thermische Ablationsverfahren Gallenwege schädigen und die Komplikationsrate der RFA bei zentral situierten Tumoren deutlich ansteigt [28,29]. Daher sollten Zielläsionen mit einem Abstand von < 1 cm von einem zentralen Gallenweg nicht mittels einer thermalen Ablation behandelt werden, um biliäre Komplikationen zu vermeiden [30]. Hilusnahe Tumore haben generell eine höhere Komplikationsrate und zudem höhere Rezidivrate [31]. In frühen RFA Studien wurde bereits gezeigt, dass die Rezidivrate substantiell mit der Tumorgröße korreliert und dementsprechend die lokale Tumorkontrollrate über 3 cm deutlich abnimmt. Erklärungen dafür sind unregelmäßige Begrenzungen größerer, teils polyglobulärer Tumore, mikroskopische Tumorausbreitung bzw. Satellitenmetastasen sowie das bereits erwähnte, begrenzte Ausmaß der Koagulationsnekrose.

Die technischen Limitationen thermaler Ablation, insbesondere ihres populärsten Vertreters der RFA, zu überwinden war ein Anreiz für die (Weiter-) Entwicklung der Brachytherapie und deren polytope, perkutane, komplikationsarme Anwendbarkeit. Die Methodik der iBT wurde eingangs bereits beschrieben.

Die Attraktivität der iBT basiert auf verschiedenen Faktoren: prinzipiell kein Größenlimit wie bei thermalen Ablationsverfahren oder der Stereotaxie (SBRT), wiederholte Anwendbarkeit an differenten Lokalisationen oder bei Rezidiven, Verwendbarkeit neben eher sensiblen Strukturen wie Gallenwegen oder dem Leberhilus, hohe Präzision in Dosierung und Verteilung, die Einzeitigkeit der unfraktionierten Bestrahlung sowie nicht zuletzt die vergleichsweise niedrigen Kosten

und die Kürze der erforderlichen Hospitalisation in Abhängigkeit der wenig frequenten Komplikationen. Zentrale bzw. hilusnahe Lebertumoren können, entweder durch Tumorkompression oder durch Kollateralschaden bei lokaler Therapie, zur posthepatischen Cholestase führen. Erfahren zentrale Gallenwege im Rahmen einer iBT hohe Punktdosen an Strahlung (Schwellendosis ca. 20,8 Gy), so können sich im kurz- oder langfristigen Verlauf (Median ca. 17 Monate) Gallenwegsstrikturen entwickeln, die zu einer posthepatischen Cholestase führen [32].

Die vorliegende Arbeit beschäftigt sich insbesondere mit der Effektivität der iBT bei der Behandlung von Metastasen dreier Tumorentitäten: Adenokarzinom des Magens, GIST und duktales Adenokarzinom des Pankreas.

Präklinische Studien haben erwiesen, dass PDAC in der Regel von Beginn an mikrometastatische, bildmorphologisch okkulte Absiedelungen ausbildet [33,34]. Dies erklärt die häufig zeitnahe metachrone Metastasierung nach Resektion des Primarius (Whipple, PPPD, Pankreaslinksresektion). In unserem Patientenkollektiv hatten 14 von 16 Patienten eine Operation des Primarius vor der iBT; 11 Patienten hatten eine metachrone und 5 Patienten eine synchrone (präoperativ bildmorphologisch okkulte) Metastasierung. Zwölf Patienten hatten einen ECOG PS von 2, was die therapeutischen Optionen laut Leitlinien auf Gemcitabine Monotherapie beschränkt. Da die Tumorerkrankung der Patienten unter palliativer Chemotherapie progredient war, kam die iBT als Salvage Manöver zur Anwendung. Im Ergebnis stand ein medianes Gesamtüberleben nach iBT von 8,9 Monaten bei einer lokalen Tumorkontrolle von 87%. Eine vergleichbare iBT Studie zum PDAC lieferte ähnliche Werte [35]. Studien zur chirurgischen Resektion sind rar; PDAC Metastasektomie erfolgt in aller Regel lediglich bei (bildmorphologisch) okkulten, synchronen Metastasen, welche bei der Operation des Primarius intraoperativ detektiert werden. Eine solche Publikation von Klein et al. (n=22) zur Resektion des PDAC Primarius mit synchroner Metastasektomie erbrachte ein medianes Gesamtüberleben von 7,6 Monaten [36]. Andere kleinere Studien veröffentlichten ein medianes Gesamtüberleben zwischen 5-8 Monaten nach Resektion meta- oder synchroner PDAC Metastasen. Thermale Ablationen bergen ein erhöhtes Risiko für biliäre Komplikationen, insbesondere bei Vorliegen einer biliodigestiven Anastomose (BDA). Eine der wenigen Studien zum Thema RFA von Park et al. bei PDAC Metastasen schlussfolgerte, dass Patienten mit kleinen (< 2cm) und wenigen Metastasen nach lokaler Ablation einen Überlebensvorteil haben [37]. Solange bis die Erfolge lokaler

Therapien beim PDAC mittels RCTs validiert werden, sollte die aktuelle Therapierationale darin bestehen, geeignete Patienten zu selektieren und die palliative Chemotherapie mit der Lokaltherapie zu kombinieren, um das Gesamtüberleben zu verlängern – im Idealfall im Rahmen eines Studieneinschlusses.

Das Adenokarzinom des Magens wird meist bereits im fortgeschrittenen Stadium diagnostiziert. Das mediane Gesamtüberleben im metastasierten Stadium beträgt mit palliativer Chemotherapie ca. 11 Monate. In diesem Stadium sind sowohl Gastrektomie als auch Metastasektomie experimentell, da bislang jegliche Evidenz aus prospektiv, randomisierten Studien fehlt. Dennoch postuliert eine veröffentlichte Metaanalyse von 39 Studien und 991 Patienten von Markar et al. [38] ein signifikant verlängertes Überleben nach chirurgischer Metastasenresektion. Zu einem ähnlichen Schluss bezüglich eines oligometastatischen (< 5 Lebermetastasen) Magenkarzinoms kommen die unrandomisierte FLOT3 Studie (31.3 Monate mit Resektion, 15,9 Monate ohne Resektion) sowie mehrere retrospektive Studien [39]. Guner et al. verglichen Leberresektion (n=68) mit RFA (n=30) in einem Kollektiv von 98 Magenkarzinom Patienten und fanden keinen signifikanten Unterschied im Outcome – das mediane Gesamtüberleben war 24 Monate (Resektion) und 23 Monate (RFA) [40]. Ein genereller Nachteil eines chirurgischen Ansatzes stellt die höhere Morbidität und Mortalität, zum Teil abhängig von Alter und Komorbiditäten der Patienten, dar. Studien, welche die Magenkarzinom Metastasenchirurgie thematisieren, berichten bis zu 26,7% Major-Komplikationen [41]. Demgegenüber steht die Therapieoption mittels iBT, welche in unserer Studie zum Einsatz kam. Eine kumulierte Anzahl von 36 Metastasen wurde mittels iBT bestrahlt; nur ein Patient hatte eine CTCAE Grad III Komplikation (Leberabszess), welche erfolgreich behandelt wurde. Die Patienten hatten vor der iBT bereits palliative Chemotherapie erhalten. Das mediane Gesamtüberleben nach iBT war 11,4 Monate, vom Zeitpunkt der Erstdiagnose 33,5 Monate. Dieser Überlebensvorteil von selektierten Patienten deckt sich mit den Beobachtungen der oben genannten Publikationen zur lokalen Therapie vom oligometastatischen Magenkarzinom. Diese Indizien müssen noch durch RCTs validiert werden, um ein systematisch aggressiveres Vorgehen beim metastasierten Adenokarzinom des Magens zu rechtfertigen.

Hingegen wird eine bereits etwas forschere Herangehensweise in den Leitlinien zu den eher seltenen GIST Tumoren empfohlen. Es stehen mittlerweile verschiedene

systemische TKI Inhibitoren zur Verfügung, welche im Wechsel bzw. in verschiedenen Therapielinien zum Einsatz kommen können. Die ESMO und NCCN Guidelines empfehlen im oligometastatischen Stadium eine Fortführung der Systemtherapie bei komplementärem Einsatz einer lokalen Therapie – genannt werden explizit chirurgische Resektion, RFA und (Chemo-)Embolisation. Ein Anreiz für die lokale Therapie stellt die primäre und sekundäre TKI Resistenz dar, welche üblicherweise innerhalb der ersten 24 Monate der TKI Therapie auftreten kann und auf der Entwicklung von sekundären Genmutationen basiert. Das Gesamtüberleben vom oligometastatischen GIST wurde in drei verschiedenen Studien ab Diagnose zwischen 45 und 57 Monaten quantifiziert [42]. Das mediane Gesamtüberleben in unserer Studie nach iBT liegt bei 37,3 Monaten, vom Zeitpunkt der Erstdiagnose 107 Monate. Insgesamt wurden 10 Patienten therapiert, welche in Summe 30 Lebermetastasen und 10 peritoneale Tumorknoten entwickelt hatten. Raut et al. publizierten Ergebnisse einer Studie zum Thema oligometastasierter GIST Metastasenchirurgie bei gleichzeitiger TKI Therapie und kamen auf ein Gesamtüberleben von 29.8 Monaten [43]. Eine Studie zur Therapie von GIST Metastasen mittels intraoperativer RFA von Pawlik et al. zeigte ein medianes Gesamtüberleben von 47,2 Monaten [44]. Die Erfolge der Studie wurden von den Autoren den strengen Einschlusskriterien mit einer Tumorgröße < 3 cm sowie prä- und postoperativer TKI Therapie zugeschrieben. Die Ergebnisse der Studien bzw. der differenten Methodiken sind aufgrund der Heterogenität der Patienten Populationen lediglich bedingt vergleichbar. Das Ziel einer lokalen Therapie beim oligometastatischen GIST besteht in einer Unterbindung oder zumindest Verzögerung einer TKI Resistenz durch Zytoreduktion und damit Verlängerung des Gesamtüberlebens. Je mehr Tumorzellen gegenüber der TKI Therapie exponiert werden und je höher die Mitoserate der Tumoren, desto größer ist die Wahrscheinlichkeit einer molekularen Evolution mit Entwicklung einer TKI Resistenz und damit einer klonalen Selektion.

Limitationen der drei Publikationen sind das einarmige, retrospektive Studiendesign sowie die geringen Patientenzahlen. Dieses Manko liegt jedoch fast allen Studien zum Thema lokale Ablationen zugrunde und kann nur durch Validierung der jeweiligen Methodik durch größer angelegte, prospektive, randomisierte, mehrarmige (ggf. multizentrische) Studien adäquat adressiert werden. Diese Problematik wird auch regelmäßig auf unterschiedlichen Kongressen aufgegriffen. Die lokale Ablation

hängt ganz allgemein vom ausführenden Interventionsradiologen sowie den unterschiedlichen verwendeten Devices und der Art der Bildführung ab, was das Design einer groß angelegten (multizentrischen) Studie zusätzlich erschwert.

Die iBT Einschlusskriterien unserer Studien sind sehr breit gefasst, da die Ziele eine Verlängerung des Gesamtüberlebens sowie die Evaluierung der Effektivität der Brachytherapie waren. Dies hat ein relativ heterogenes Patientenkollektiv zur Folge, da die Patienten in unterschiedlichem Maße vortherapiert waren, was jedoch letztlich ein zu vernachlässigender Faktor ist, weil sich alle Patienten zum Zeitpunkt der iBT ohnehin in einer Salvage Situation befanden. Der Nachbeobachtungszeitrum unterliegt interindividuell einigen Fluktuationen – ein Problem, welches bei der Initiierung einer prospektiven Studie zu lösen sein sollte. Die überwiegende Mehrheit an lokalen Progressionen nach iBT wird typischerweise innerhalb der ersten 12 Monate nach iBT beobachtet und ist in erster Linie einer Unterdosierung des Tumorrandes geschuldet.

4. Zusammenfassung

IBT repräsentiert eine effektive, kosteneffiziente und sichere Alternative im antineoplastischen Arsenal der lokalen Therapiemaßnahmen bzw. der interventionellen Onkologie und ermöglicht durch die Erweiterung des Therapiespektrums die Erstellung zunehmend individualisierter, multimodaler Konzepte für Patienten im (oligo-)metastasierten Tumorstadium verschiedenster Tumorentitäten.

Bei selektierten Patienten suggerieren unsere Studien-Ergebnisse einen Überlebensvorteil im metastasierten Stadium durch Tumorkontrolle und Zytoreduktion mittels iBT. Bei allen drei untersuchten Tumorentitäten konnten hohe lokale Tumorkontroll-Raten durch die Applikation der iBT erzielt werden. Die lokale Kontrolle beim metastasierten PDAC belief sich auf 87%, das mediane Gesamtüberleben nach iBT auf 8,9 Monate. Analog dazu wurden auch hohe lokale Kontrollraten beim metastasierten Adenokarzinom des Magens (89%) sowie beim metastasierten GIST (97,5%) erreicht. Das mediane Gesamtüberleben der Magenkarzinom Patienten (nach iBT) war 11,4 Monate, das mediane Gesamtüberleben der GIST Patienten 37,3 Monate.

Die mediane Dauer der Hospitalisation im Rahmen der iBT betrug in allen drei Studien vier Tage. Die (Major-)Komplikationsraten (CTCAE 3+) der iBT waren gering: PDAC (3), Magenkarzinom (1), GIST (2).

Indikationen zur iBT können auch bei unresektablen oder problematisch lokalisierten Tumoren sowie Zielläsionen jenseits der Limitationen thermischer Ablationsverfahren gestellt werden.

Es besteht dringender Bedarf an prospektiven, randomisierten, mehrarmigen (ggf. multizentrischen) Studien mit größerer Fallzahl, um die vielversprechenden Ergebnisse zu validieren und den Weg für eine breitere Anwendung der iBT zu ebnen.

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6. Veröffentlichungen

1) **Drewes R**, Omari J, Manig M, Seidensticker M, Hass P, Ricke J, Powerski M, Pech M:
   Treatment of hepatic pancreatic ductaladenocarcinoma metastases with high-dose-rate image-guided interstitial brachytherapy: a single center experience. J Contemp Brachytherapy 2019; 11, 4. 1 - 8

2) Omari J, **Drewes R**, Othmer M, Hass P, Pech M, Powerski M:
   Treatment of metastatic gastric adenocarcinoma with image guided high-dose-rate, interstitial brachytherapy as second line or salvage therapy. Diagn Interv Radiol. 2019 Jul 26.

3) Omari J, **Drewes R**, Matthias M, Mohnike K, Seidensticker M, Seidensticker R, Streitparth T, Ricke J, Powerski M, Pech M:
   Treatment of metastatic, imatinib refractory, gastrointestinal stroma tumor with image-guided high-dose-rate interstitial brachytherapy. Brachytherapy. 2019 Jan - Feb;18(1):63-70.

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.

J Contemp Brachytherapy 2019; 11, 4: 329-336
DOI: https://doi.org/10.5114/jcb.2019.87269

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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Received: 20.02.2019
Accepted: 23.07.2019
Published: 29.08.2019

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.

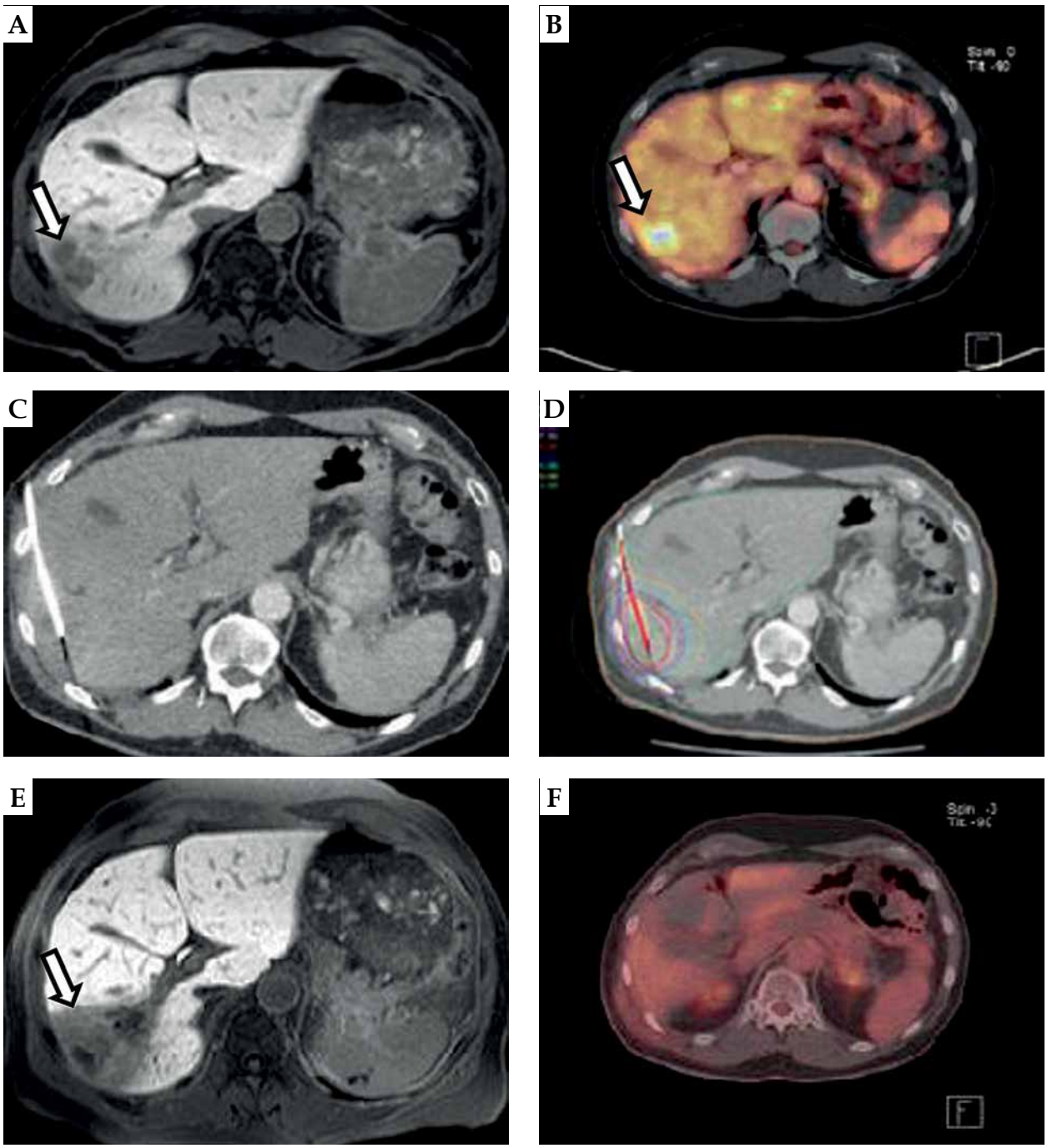

Fig. 1. Local tumor control in a patient with metastatic PDAC. **A**) Axial T1w Gd-EOB-DTPA (Primovist)-enhanced MRI (baseline MRI prior to iBT), arrow points to liver metastases; **B**) FDG-PET-CT demonstrates the activity of the hepatic lesions (arrow) prior to iBT; **C**) Inserted brachytherapy catheter 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-

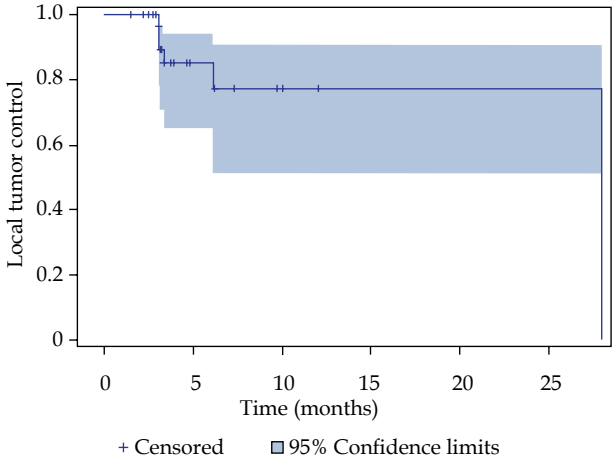

Fig. 2. Local tumor control (LTC) after iBT of pancreatic ductal adenocarcinoma (PDAC) metastases, estimated with the Kaplan Meier method

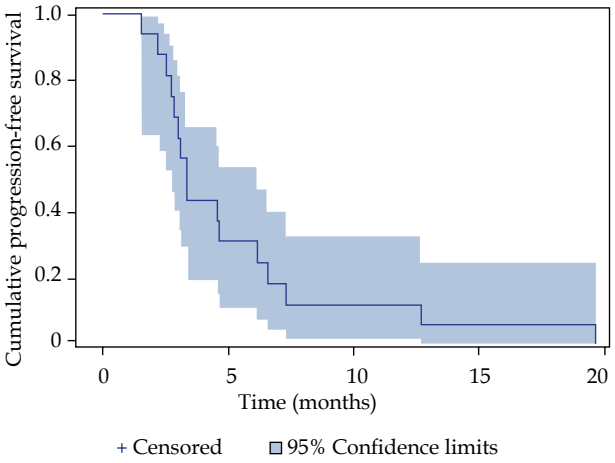

Fig. 3. Progression-free survival (PFS), calculated from the time of iBT, of patients with metastatic PDAC after treatment with iBT, estimated with the Kaplan Meier method

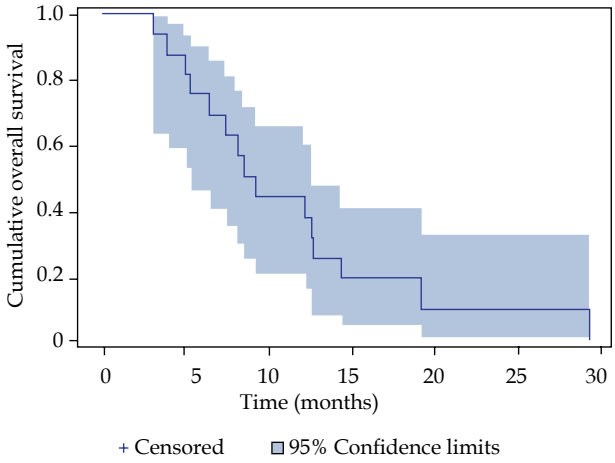

Fig. 4. Overall survival (OS), calculated from the time of iBT, of patients with metastatic PDAC ablated with iBT, estimated with the Kaplan Meier method

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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Diagn Interv Radiol DOI 10.5152/dir.2019.18390

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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Maciej Pech
Maciej Powerski

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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Received 29 August 2018; revision requested 28 September 2018; last revision received 18 January 2019; accepted 31 January 2019.

Published online 23 July 2019.

DOI 10.5152/dir.2019.18390

You may cite this article as: Omari J, Drewes R, Othmer M, Hass P, Pech M, Powerski M. Treatment of metastatic gastric adenocarcinoma with image-guided high-dose rate, interstitial brachytherapy as second-line or salvage therapy. Diagn Interv Radiol 2019; DOI 10.5152/dir.2019.18390.

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.

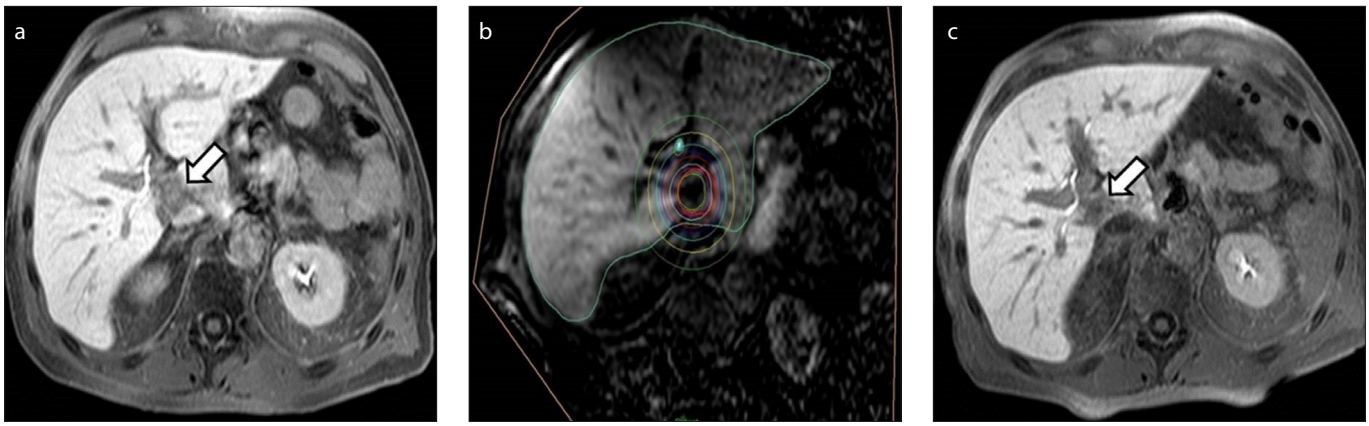

Figure 1. a–c. Local tumor control in a patient with metastatic gastric adenocarcinoma. Axial Gd-EOB-DTPA enhanced T1-weighted image **(a)** shows metastasis from gastric adenocarcinoma prior to treatment with iBT *(white arrow)*; axial Gd-EOB-DTPA enhanced T1-weighted image **(b)** shows treatment planning 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.

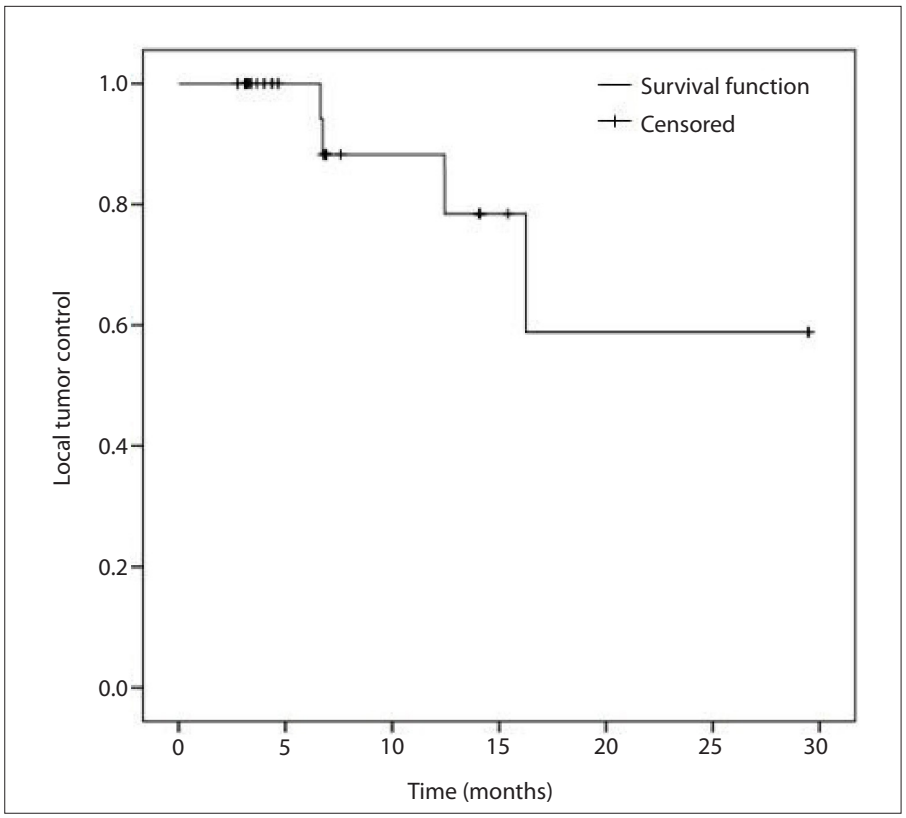

Figure 2. Local tumor control after iBT.

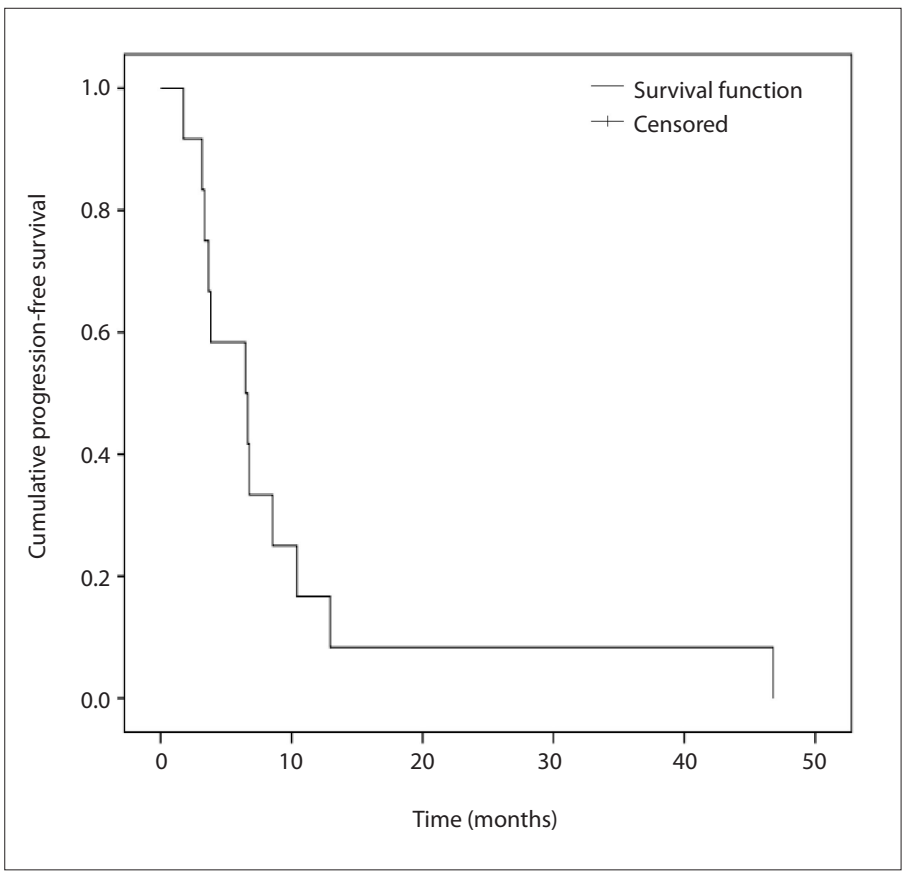

Figure 3. Progression-free survival of all patients with metastatic gastric adenocarcinoma treated with iBT.

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

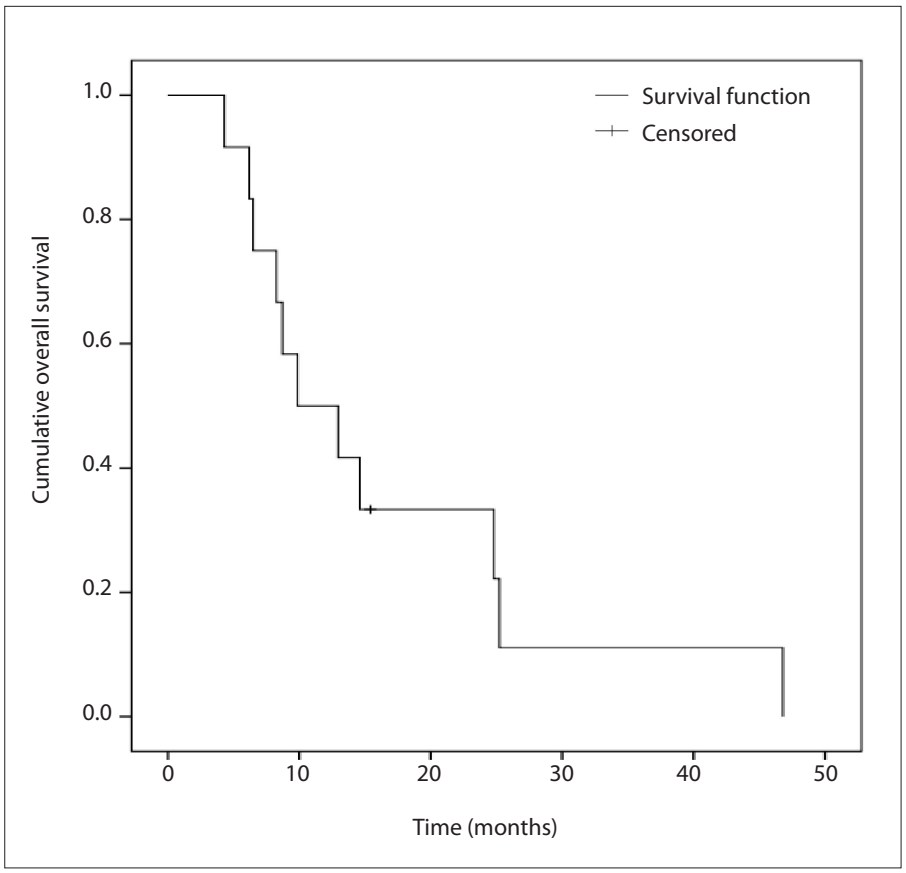

Figure 4. Overall survival of all patients with metastatic gastric adenocarcinoma ablated by iBT.

(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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BRACHYTHERAPY

Brachytherapy 18 (2019) 63–70

Gastrointestinal Oncology

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

Received 2 July 2018; received in revised form 12 September 2018; accepted 25 September 2018.

Conflict of interest: No author has any conflict of interest to declare.

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1538-4721/$ - see front matter
https://doi.org/10.1016/j.brachy.2018.09.006

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 (≤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

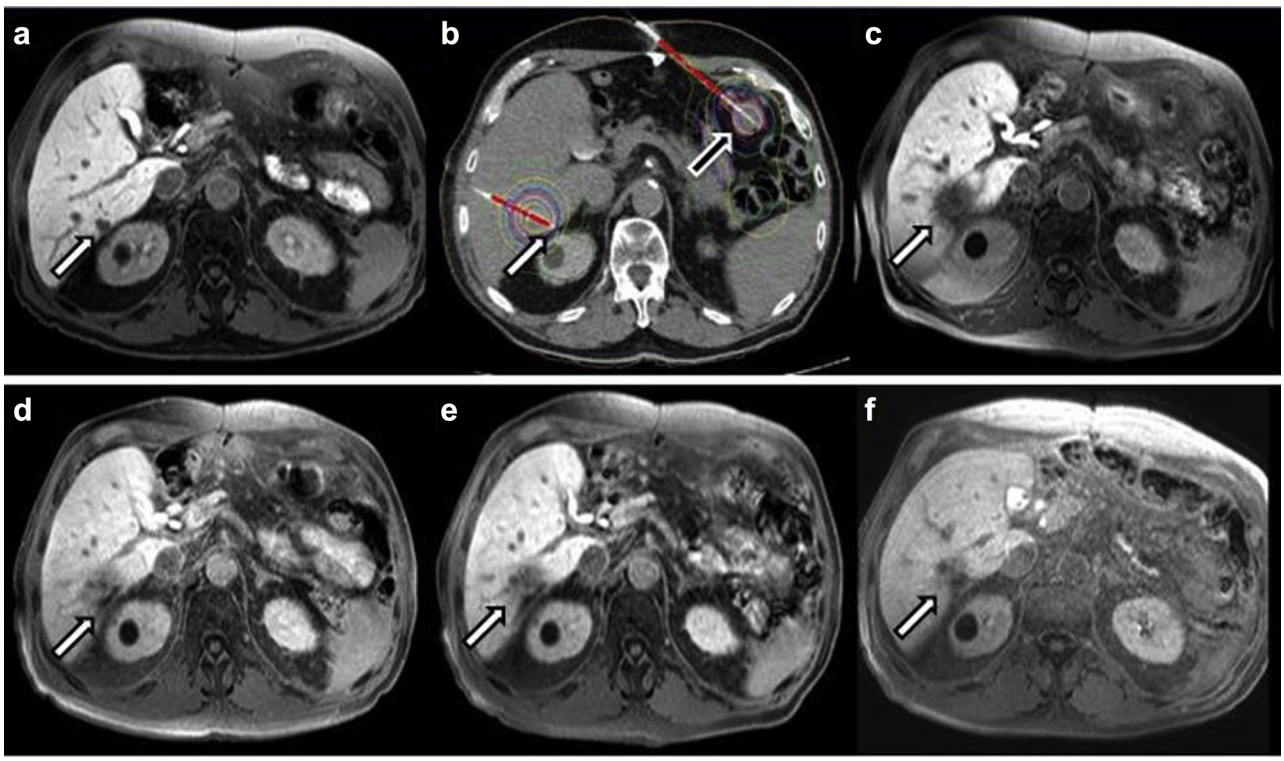

Fig. 1. (a): Baseline Gd-EOB-DTPA enhanced T1w MRI. White arrow indicates gastrointestinal stroma tumor metastasis in liver segment 6. (b) Demonstrates inserted brachytherapy catheters in the liver lesion (white arrow) and in a second extrahepatic peritoneal lesion (black arrow). Lines represent isodoses 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,

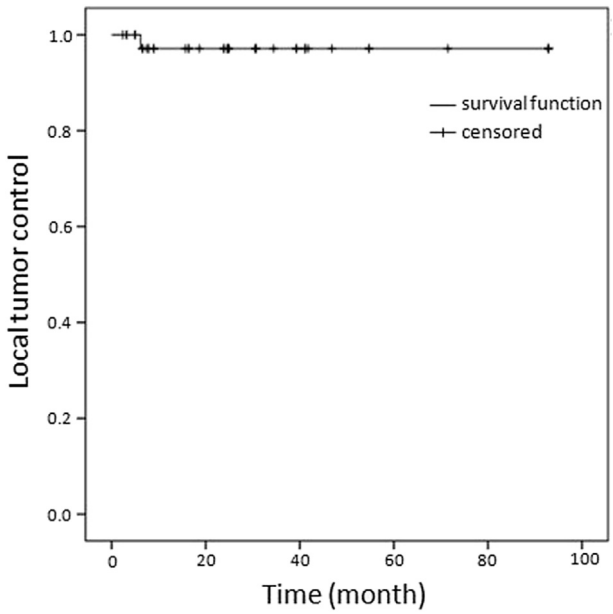

Fig. 2. Local tumor control after iBT of gastrointestinal stroma tumor metastases.

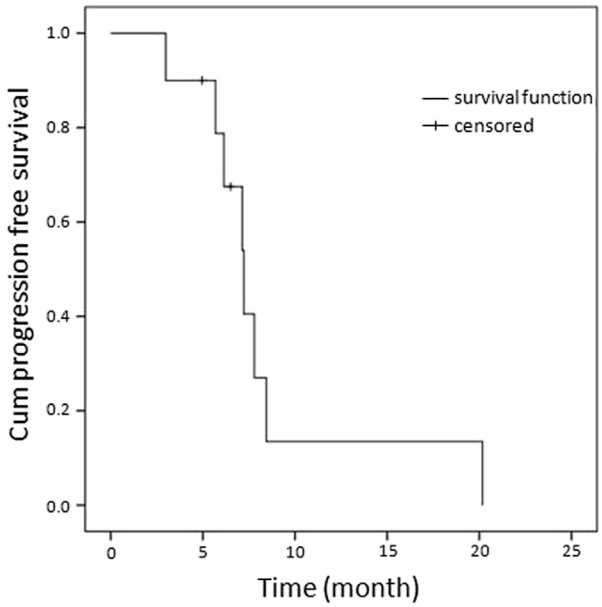

Fig. 3. Progression-free survival (calculated from the time of iBT) of patients with metastatic gastrointestinal stroma tumor after treatment with iBT.

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).

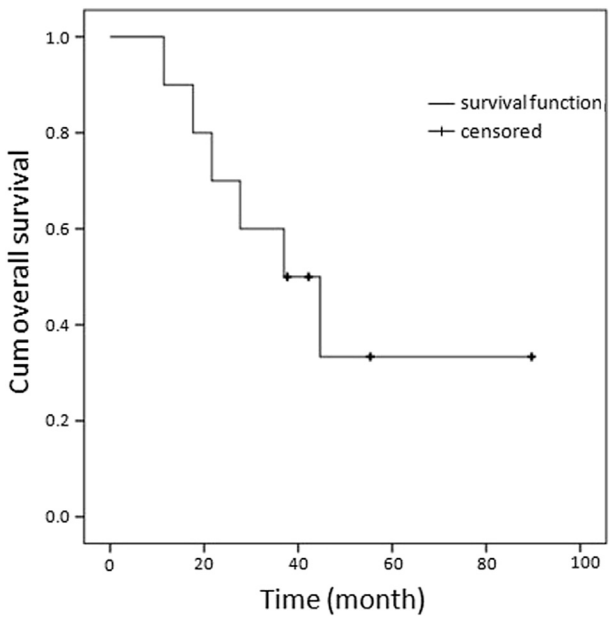

Fig. 4. Graph shows overall survival (calculated from the time of iBT) of patients with metastatic gastrointestinal stroma tumor ablated with iBT.

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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7. Appendix

7.1. Danksagung

Meine Dankbarkeit gilt dem Klinikdirektor der diagnostischen und interventionellen Radiologie des Universitätsklinikums Magdeburg Herrn Prof. Dr. M. Pech für die Unterstützung und den offenen Dialog über diverse wissenschaftliche Themengebiete inklusive einer kumulativen Promotion.

Besonderer Dank gebührt meinem Doktorvater bzw. Betreuer Herrn Professor Dr. M. Powerski, der zu jeder Zeit hilfsbereit und in unterschiedlichsten Belangen ansprechbar war. Außerdem stellte er nach einer offenen Diskussion das Thema zur Verfügung.

Darüber hinaus gilt mein Dank meinem Freund und Kollegen Herrn Dr. med. J. Omari, mit dem ich den Weg der radiologischen Weiterbildung seit Beginn an der Uniklinik Magdeburg gemeinsam beschreite.

7.2. Ehrenerklärung

Ich erkläre, dass ich die der Medizinischen Fakultät der Otto-von-Guericke-Universität zur Promotion eingereichte Dissertation mit dem Titel

Evaluierung der Effektivität der bildgeführten, interstitiellen HDR-Brachytherapie in der Behandlung gastrointestinaler, hepatisch und peritoneal metastasierter Tumorentitäten.

in der Klinik für Radiologie und Nuklearmedizin der Medizinischen Fakultät der Otto-von-Guericke-Universität Magdeburg

mit Unterstützung durch Herrn Prof. Dr. med. M. Powerski

ohne sonstige Hilfe durchgeführt und bei der Abfassung der Dissertation keine anderen als die dort aufgeführten Hilfsmittel benutzt habe.

Bei der Abfassung der Dissertation sind Rechte Dritter nicht verletzt worden.

Ich habe diese Dissertation bisher an keiner in- oder ausländischen Hochschule zur Promotion eingereicht. Ich übertrage der Medizinischen Fakultät das Recht, weitere Kopien meiner Dissertation

herzustellen und zu vertreiben.

Magdeburg, 24.11.2019

Unterschrift

7.3. Erklärung zur strafrechtlichen Verurteilung

Ich erkläre hiermit, nicht wegen einer Straftat verurteilt worden zu sein, die Wissenschaftsbezug hat.

Magdeburg, 24.11.2019

Unterschrift

8. Anhang

Lebenslauf

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