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DISSERTATION

Analyse der verschiedenen intrahepatischen Progressionsmuster bei Leberkrebs

Analysis of different intrahepatic progression patterns in liver cancer

zur Erlangung des akademischen Grades

Doctor rerum medicinalium (Dr. rer. medic.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

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Datum der Promotion: 29.11.2024

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List of abbreviations

HCC: hepatocellular carcinoma

CRLM: colorectal cancer liver metastases

CT: computed tomography

MRI: magnetic resonance imaging

OS: overall survival

PFS: progression-free survival

TTP: time to progression

HIPAA: Health Insurance Portability and Accountability Act

RECIST: Response Evaluation Criteria in Solid Tumors

PFS_{local}: progression-free survival with local recurrence (subtype of PFS)

$PFS_{distant}$: progression-free survival with intrahepatic distant progression (subtype of PFS)

TTP_{local}: time to progression with local recurrence (subtype of TTP)

$TTP_{distant}$: time to progression with intrahepatic distant progression (subtype of TTP)

CI: confidence interval

HR: hazard ratio

RFA: radiofrequency

MWA: microwave ablation

BCLC: Barcelona Clinic Liver-Cancer

SBRT: stereotactic whole-body radiotherapy

CLIP: Cancer of the Liver Italian Program

TACE: Transcatheter arterial chemoembolization

ALT: alanine aminotransferase;

AP: alkaline phosphate;

AST: aspartate aminotransferase

CR: complete response

PR: partial response

SD: stable disease

PD: progressive disease

Abstract

Introduction: Given current detection strategies for patients receiving brachytherapy do not consider the underlying cancer entity and little is known about its sensitivity to malignancy to brachytherapy. The aim of this study was to use vertical multi-parameter MRI to carry out the survival conclusions of hepatocellular carcinoma (HCC) and colorectal cancer liver metastases (CRLM) after computed tomography (CT)-guided high-dose-rate brachytherapy.

Patients and methods: 114 HCC and 50 CRLM patients only treated with brachytherapy from January 2016 to January 2018 were identified and included in this retrospective analysis. Baseline patient, tumor, and other related characteristics collected. All multiparametric magnetic resonance images collected before, and about 8 weeks after brachytherapy, then every 3 months for the first year, and every 6 months for the following years, the endpoints of this analysis were any progressions or death. RECIST 1.1 were assessed by MRI scans. The overall progression-free survival (PFS) was the primary endpoint. Specifically, local and distant intrahepatic PFS were identified and assessed to determine differences between the intrahepatic progression patterns of HCC and CRLM. The predictors of PFS were the secondary endpoints. Kaplan-Meier analysis and univariate and multivariate Cox regression modeling were used for statistics analysis.

Results: A total of 131 and 56 completed brachytherapy treatments were performed in HCC and CRLM patients and a total of 114 HCC patients enrolled in this study received an average of 3.11 ± 1.80 imaging follow-up scans, and 50 CRLM patients received 2.36 ± 1.64 scans. The median overall PFS was longer in HCC [11.30 (1.33-35.37) months] than in CRLM patients [8.03 (0.73-19.80) months; p = 0.048]. The local recurrence of progression-free survival (PFSlocal) was apparently longer in HCC [36.83 (1.33-40.27) months] than in CRLM patients [12.43 (0.73-21.90) months; p = 0.001] Multivariate Cox regression confirmed tumor type and patient age as independent predictors of PFS.

Conclusion: Brachytherapy proved to achieve good local control of both HCC and CRLM. Local tumor recurrence was observed earlier in CRLM as compared to HCC patients. But in HCC, distant progression preempted local recurrence. The findings may help design disease-specific monitoring strategies for different tumor entities following brachytherapy. The results can improve personalized treatment planning including combinations of loco-regional and immuno-oncological therapies.

Zusammenfassung

Einleitung: Die derzeitigen Erkennungsstrategien für Patienten, die eine Brachytherapie erhalten, berücksichtigen nicht die zugrundeliegende Krebsentität, und es ist wenig über die Empfindlichkeit gegenüber Malignität oder das Risiko einer malignen chemischen Reaktion auf die Brachytherapie bekannt. Ziel dieser Studie war es, mit Hilfe der vertikalen Multiparameter-MRT das Überleben von hepatozellulären Karzinoms (HCC) und der Lebermetastasen des kolorektalen Karzinoms (CRLM) nach computertomographisch (CT) gesteuerter Hochdosis-Brachytherapie zu bewerten.

Patienten und Methoden: 114 HCC- und 50 CRLM-Patienten, die von Januar 2016 bis Januar 2018 ausschließlich mit Brachytherapie behandelt wurden, wurden identifiziert und in diese retrospektive Analyse aufgenommen. Grundlegende Patienten-, Tumor- und andere damit verbundene Merkmale wurden erfasst. Alle multiparametrischen Magnetresonanzbilder wurden vor und etwa 8 Wochen nach der Brachytherapie, dann alle 3 Monate für das erste Jahr und alle 6 Monate für die folgenden Jahre erhoben. Die Endpunkte wurden anhand von MRT-Scans nach RECIST 1.1 bewertet. Das gesamte progressionsfreie Überleben (PFS) war der primäre Endpunkt. Insbesondere wurden das lokale und das entfernte intrahepatische PFS ermittelt und bewertet, um Unterschiede zwischen den intrahepatischen Progressionsmustern von HCC und CRLM festzustellen. Die Prädiktoren für das PFS waren die sekundären Endpunkte. Für die statistische Analyse wurden die Kaplan-Meier-Analyse sowie die univariate und multivariate Cox-Regressionsmodellierung verwendet.

Ergebnisse: Insgesamt wurden 131 und 56 abgeschlossene Brachytherapie-Behandlungen bei HCC- und CRLM-Patienten durchgeführt. 114 HCC-Patienten, die an dieser Studie teilnahmen, erhielten im Durchschnitt 3,11 ± 1,80 bildgebende Nachuntersuchungen, 50 CRLM-Patienten 2,36 ± 1,64 Untersuchungen. Das mediane Gesamt-PFS war bei HCC-Patienten länger [11,30 (1,33-35,37) Monate] als bei CRLM-Patienten [8,03 (0,73-19,80) Monate; p = 0,048]. Das lokale Wiederauftreten des progressionsfreien Überlebens (PFSlocal) war bei HCC offenbar länger [36,83 (1,33-40,27) Monate] als bei CRLM-Patienten [12,43 (0,73-21,90) Monate; p = 0,001] Die multivariate Cox-Regression bestätigte den Tumortyp und das Patientenalter als unabhängige Prädiktoren für das PFS.

Schlussfolgerung: Mit der Brachytherapie konnte sowohl bei HCC als auch bei CRLM eine gute lokale Kontrolle erreicht werden. Ein lokales Tumorrezidiv wurde bei CRLM-Patienten früher als bei HCC-Patienten beobachtet. Bei HCC ging jedoch die Fernprogression dem Lokalrezidiv voraus. Die Ergebnisse können helfen, krankheitsspezifische Überwachungsstrategien für verschiedene Tumorentitäten nach einer Brachytherapie zu entwickeln. Die Ergebnisse können die personalisierte Behandlungsplanung verbessern, einschließlich der Kombination von lokoregionalen und immunonkologischen Therapien.

1 Introduction

1.1 Liver cancer

Malignant tumors of the liver are commonly referred to as liver cancer, either primary or secondary, with approximately 841,000 new cases each year and 782,000 deaths, ranking as the fourth leading cause of cancer death worldwide and mainly distributed in East Asia, Southeast Asia, and West Africa (⩾6.4%).[1] Hepatocellular carcinoma (HCC) accounts for 75%-80% of primary liver cancers, and most patients with HCC are initially diagnosed at an intermediate to terminal stage and have lost the opportunity for curative treatment, making it a major global health concern.[2, 3] According to the latest statistics, 41,260 new liver cancer patients are expected to be diagnosed in 2022, resulting in the fifth-highest number of 30,520 deaths.[4] Also, cancer metastasis from another organ occurs frequently in the liver, including colorectal cancer liver metastasis (CRLM). Approximately 20-30% of colorectal cancer patients already have liver metastases at the time of diagnosis, and many others develop liver metastases after surgery or during treatment; overall, 50%-70% of colorectal cancer patients will have liver metastases.[5]

1.2 Treatment strategy for liver cancer

Surgical treatment of hepatocellular carcinoma is an essential tool for patients with hepatocellular carcinoma to achieve long-term survival, mainly including hepatectomy and liver transplantation. In terms of radical treatment of liver cancer, surgery is considered to be the best option, but some patients cannot tolerate surgical treatment due to the combination of most patients with different degrees of cirrhosis. Ablation therapy, which has been widely used, has less impact on liver function, less trauma, and exact efficacy. Ablation therapy is applicable to Barcelona clinic liver cancer (BCLC) stage ia and some stage ib hepatocellular carcinomas (i.e., a single lesion with a maximum diameter of 5 cm; or 2-3 lesions with a maximum diameter of 3 cm) and can obtain radical treatment effect. Surgical resection of multiple or single lesions with a maximum diameter of 3-6 cm should be used in combination with other treatments.[6] To patients with HCC with a maximum diameter of ⩽3 cm, ablation therapy achieves similar or slightly lower progression-free survival rates and overall survival rates than surgical resection but lower side-effects rate and length of stay than surgical resection. For individual hepatocellular

carcinoma with a maximum diameter ⩽2 cm, the efficacy of ablative therapy is similar to that of surgical resection, especially for central HCC.[7] CT-guided high-dose-rate brachytherapy (CT-HDRBT) is an internal radiation therapy in which a radioactive source such as Iridium 192 is delivered to tumor lesions through catheters inserted into the tumor at CT.[8, 9] It is increasingly used by countries around the world, especially in Europe and the United States, and has achieved good therapeutic results in the treatment of solid primary and secondary tumors.[10] Unlike microwave ablation (MWA) and radiofrequency ablation (RFA), Brachytherapy with a broader adaptation overcomes the limitations of tumor size and its location in relation to blood vessels, etc. CRLM is one of the most intractable tumors globally due to its heterogeneity and high rate of recurrence. Despite a multidisciplinary approach, patients with CRLM have a limited five-year survival rate.[11] Because of the risk of systemic adverse reactions, even the most commonly used chemotherapy had a life-prolonging effect for CRLM patients for 2-3 months.[12] Minimally invasive local treatment is an effective option for liver disease with low surgical risk and probability of adverse events.[13] The overall survival (OS) with local thermal ablation techniques is similar to that for hepatectomy. The effectiveness of thermal ablation is limited by the heat-sink effect, which is caused when the lesions are close to blood vessels or longer than 5 cm in diameter.[14] In addition, given the irradiation dose of liver cancer, is closely related to the survival time and local control rate of patients, it basically depends on the tolerated dose of surrounding normal tissues. Stereotactic radiotherapy is generally recommended to be 45-60 Gy/3-10 fractions (Fx), with radiotherapy bioequivalent dose ⩾ 80 Gy. By planning precise 3D radiotherapy and rapidly reducing doses outside of the target tissue, brachytherapy can deliver high doses of radiation to tumors at a single site (100 Gy at the center of the tumor), while the surrounding the liver parenchyma is not affected and removed immediately after treatment.[15] This intervention has high safety and low complication rate for patients, and the local tumor control rate is promising. In addition, brachytherapy has the potential to inhibit the development of other lesions in the liver due to distal effects. Therefore, it is a more important option than surgery in the treatment of patients with advanced liver tumors, especially when patients have a declined liver function or chronic liver disease and cannot tolerate surgical treatment. Considering this, brachytherapy is also appropriate for patients with multifocal (>3) or large (>5 cm) unresectable HCC with a median OS of 28.8 and a time to progression (TTP) of 11.6 months.[16]

1.3 Monitoring strategies after brachytherapy

However, current detection strategies for patients receiving brachytherapy do not consider the underlying cancer entity. Beyond that, little is known about its sensitivity to malignancy or the hazard of malignancy's chemical response to brachytherapy.[17] Direct evidence applies the underlying theory that most attacks are limited to the liver and occur within the first year after treatment. Although this seems reasonable in judgment, there have been no previous reports on the analysis of HCC and CRLM, and there is no scientific research to further study the progress of intrahepatic malignancies in special circumstances, especially to analyze the types of intrahepatic malignancies, which will greatly assist the patient's efficacy and the design of treatment strategies. Since the ultra-primary and the multi-location onset of HCC and CRLM is likely to require precise medical detection and treatment, the purpose of this analysis is to use vertical multi-parameter MRI to carry out the survival conclusion of HCC and CRLM after brachytherapy. Three-dimensional imaging (MRI) of its special intrahepatic part and distant progress.

2 Methods

This research was originally published in the journal of Therapeutic Advances in Medical Oncology. Xu, H., Schmidt, R., Hamm, C. A., Schobert, I. T., He, Y., Böning, G., Jonczyk, M., Hamm, B., Gebauer, B., & Savic, L. J. (2021). Comparison of intrahepatic progression patterns of hepatocellular carcinoma and colorectal liver metastases following CT-guided high dose-rate brachytherapy. Ther Adv Med Oncol., 13, 17588359211042304. https://doi.org/10.1177/17588359211042304

The following text describes the already published Methods in detail.

2.1 Study cohort and endpoints

This single-institution retrospective study complied with the Health Insurance Portability and Accountability Act (HIPAA) and was approved by the Institutional Review Board (EA4/089/17). Because of the retrospective analysis of the observational study design, no informant agreement was collected. The treatment of HCC and CRLM patients was discussed by a multidisciplinary tumor board and brachytherapy was recommended. The study enrolled consecutive patients with HCC and CRLM who underwent brachytherapy from January 2016 to January 2018. All patients in the sequence received a baseline MRI scan at least once within 30 days before brachytherapy and a posterior MRI scan approximately 8 weeks after brachytherapy. A locoregional, minimally invasive, liver-oriented treatment was applied to all target lesions. The aim of treatment is to reduce local recurrence or distant metastases and prolong tumor-free survival of patients. The primary endpoint was progression-free survival (PFS). Specifically, we assessed the intrahepatic local and distant PFS using follow-up MRIs in order to examine differences in intrahepatic progression between HCC and CRLM. The predictors of OS, PFS, and TTP were identified as secondary endpoints.

2.2 CT-guided high dose-rate brachytherapy

Interventional radiologists responsible for the treatment had 12 and 8 years of experience with brachytherapy, respectively. Patients were treated lying flat on the examination bed of CT, with local sterilized, under anesthetic (1 mg midazolam and 75 g fentanyl, with 25 g fentanyl or 1 mg midazolam administered intravenously in increasing doses, depending on each patient's individual level of pain or discomfort) and local anesthesia (xylocaine).

Under CT-fluoroscopic guidance and puncture of the tumor with a 14-gauge needle, a 6F diameter angiographic sheath (Radiofocus; Terumo, Japan) was inserted over a rigid angiographic guidewire (Amplatz, Boston Scientific, Boston, MA) through which a 6F closed-end brachytherapy catheter (Primed, Halberstadt, Germany). To confirm the treatment plan, after the catheter tip was positioned inside the tumor, the patient was temporarily occluded and a spiral CT of the liver was enhanced by intravenous injection of iodine contrast (100 mL; Ultravist 370; flow rate, 1 mL/sec; initiation delay, 80 s). Contrast-enhanced CT scans (5mm reconstructed slices), a 3D radiation planning workstation, and the catheter's relative position to the tumor enabled further treatment planning (Brachyvision; Varian Medical Systems, Palo Alto, CA, USA.) The portal venous phase for CRLM was chosen (45 s after injection), and the arterial phase for HCC (15 s after injection). Treatment planning was set up in Abacus 3.0 software, mainly to determine the relative coordinates of the catheter and tumor and to delineate dose boundaries for the catheter target, with the aim of ablating each lesion using the Iridium-192 source (Gammamed 12; Varian Medical Systems) at a tumor-encircling target dose of 20 Gy. To avoid risking damage to adjacent structures, we mark the adjacent organs and calculate the dose. The puncture channel is closed with an absorbable thrombogenic material after withdrawal of the radiation source to avoid hemorrhage after completion of treatment. If multiple tumors are required for treatment, brachytherapy is considered complete when all target lesions have been fully irradiated to a target dose of 20 Gy. Interventional radiologists will schedule and select the appropriate lesions at their discretion. If one patient is found to have multifocal or larger tumors at baseline, and a single treatment session is not sufficient, more treatment sessions were required to avoid adverse events associated with tumor lysis or to reduce the risk of cumulative punctures. Therefore, patients who received up to 4 consecutive brachytherapy sessions at 4–6-week intervals to achieve full treatment were included. Following the first brachytherapy, patients who developed new intrahepatic lesions which had not been present at baseline during follow-up and received additional brachytherapy sessions for these new lesions (at least eight weeks after the first brachytherapy) were considered separate treatments for the purpose of TTP calculation. Nevertheless, this event was regarded as tumor progression for the purposes of calculating PFS, and follow-up for this patient ended.

2.3 MRI acquisition and analysis

MRI and RECIST protocol. Baseline and follow-up MRI images of all patients were recorded at a 1.5-T scanner (Avanto, Siemens, Erlangen, Germany) using an eight-channel phased-array coil for the body. The hepatocyte-specific contrast agent (0.25mmol/ml Primovist; Bayer, Germany) was used for dynamic contrast-enhanced sequences. Standard volume-interpolated breath-hold examination (VIBE) images were obtained according to a standard protocol with a TR of 4.26ms, a TE of 1.87ms, a flip angle (FA) of 10°, a slice thickness of 3 mm, and a matrix size of 256 x 127, covering the entire liver with 60-72 slices and an adjusted field of view (FOV) of 255-300 x 340-400 mm. Merlin Phoenix version 5.8 (Pix-meo SARL, Bernex, Switzerland) was used to analyze the images. Given not all patients had pathology results, MRI diagnostic criteria were applied. For HCC patients, multiparametric dynamic MRIs of the arterial phase (mainly in the late arterial phase) show homogeneous or heterogeneous marked enhancement of the tumor, and portal and/or delayed phase liver tumor enhancement is lower than the liver parenchyma. Multiparametric dynamic MRI scans are particularly suitable for the diagnosis of hepatocellular carcinoma with a maximum tumor diameter < 2.0 cm (<1.0 cm), emphasizing that other signs (such as envelope-like enhancement, moderate T2WI signal, and diffusion restriction) and suprathreshold growth [50% increase in the maximum diameter of the lesion within 6 months (inclusive)] should be combined. Envelope-like enhancement was defined as smooth, homogeneous, well-defined borders that mostly or completely enveloped the lesion and showed circumferential enhancement, especially in the portal, delayed, or migrated phases. For CRLM patients, MRI shows multiple or single tumor lesions in the liver with well-defined margins, often appearing as homogeneous, mildly with a low signal T1WI and high signal T2WI images. 25% of tumor sites show a high signal on T1WI and a low signal on T2WI. The signal on T2WI may be elevated around the tumor in some cases, which may be associated with edema or vascularization (Figure 2). MRI plan and tumor response assessment. Multiparametric MRIs were performed before and approximately 8 weeks after brachytherapy, then every 3 months during the first year and every 6 months during the following years until death, loss of follow-up, or the end of observation time point.

From follow-up records, two radiologists without brachytherapy experience assessed the tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[18] Target and non-target lesions are evaluated and recorded in an individual form.

After the follow-up period ended in June 2020, all MRI scans checked up until June 2020 were included in this analysis.

2.4 Survival analysis (Kaplan–Meier)

OS, PFS, TTP, and their subtypes were analyzed by using Kaplan-Meier analysis and the log-rank test.

Overall survival

OS was defined as the time between a completed brachytherapy treatment and the date of death from any cause. In the case of patients who have not been followed up with or are still alive at the time of their last follow-up without any events (progression or death) at that stage, those patients should be censored.

Progression-free survival

PFS was defined as the time between the completion of brachytherapy and death or the occurrence of tumor progression intrahepatic or extrahepatic. With additional locoregional treatment, patients were excluded at the corresponding time points. Patients were censored at the end of follow-up without any intrahepatic progressions or deaths.

Time- to- progression

TTP was defined as the time between the completion of brachytherapy and the occurrence of any intra- or extrahepatic progressions. In comparison to PFS, TTP in this study was calculated for each completed brachytherapy cycle (i.e., multiple brachytherapy sessions completed for different targets in the same patient).

Intrahepatic progression patterns.

Two specific patterns of progression were assessed separately in the subgroup analysis in addition to the overall PFS and TTP. Specifically, the subtypes of progression patterns were defined as intrahepatic local recurrence of a treated lesion (PFS_{local} or TTP_{local}) and distant intrahepatic progression ($PFS_{distant}$ or $TTP_{distant}$). The local recurrence was defined as a >20% increase in treated lesion diameter according to RECIST 1.1. PFS_{local} was assessed based on the target lesion treated at the first completion of brachytherapy (A completed treatment at the patient level), whereas TTP_{local} was assessed based on the target lesion treated at each completion of brachytherapy (A completed treatment at the

tumor level). Distant intrahepatic progression was defined as the appearance of a new malignant intrahepatic lesion at a different site and with no prior brachytherapy before.

2.5 Cox proportional hazard regression model

The specific goal of survival analysis is the relationship between the scientific research covariate (variable) X and the observation conclusion, that is, the survival function formula S(t,X). Because the survival data information includes censored data information, the above problems cannot be solved by general multiple regression analysis. A very important part of survival analysis is to explore the risk source that harms the survival time or survival rate. This risk source can harm the survival rate according to the lethal risk of each time. The risk rate function formula at the same time is different. Usually, the risk rate function formula is expressed as the multiplication of the standard risk rate function formula and the corresponding covariate function formula.

To achieve a comprehensive analysis of the results, in addition to Kaplan-Meier analysis, a univariate Cox proportional hazards regression model was added to assess the predictive value of the individual determinants (predictor variables). PFS, PFS_{local}, and $PFS_{distant}$ variables which are statistically significant ($p<0.1$) were included in the multivariate Cox proportional hazards regression model ($p<0.05$) to determine their predictive value when multiple factors are considered. Previously reported covariates affecting survival outcomes were selected.[19-22] In the Cox regression model, in addition to tumor characteristics from imaging (tumor type, diameter of target lesion, number of target lesions), baseline data from a clinical workstation and demographic parameters (age, gender) were collected from electronic medical record system before treatment.

2.6 Statistics

The data collected were calculated by SPSS 23.0 software (IBM SPSS Statistics, version 26, 2019, IBM Corp, Armonk, NY, USA), and descriptive statistical information was reported as mean ± standard deviation (SD) and mean and range, respectively. A $p < 0.05$ for survival analysis was considered statistically significant. In addition, univariate Cox regression analysis and those parameters, that achieved a $p < 0.1$ were considered for multivariate analysis, and a $p < 0.05$ were defined as statistically significant.

3. Results

This research was originally published in the journal of Therapeutic Advances in Medical Oncology. Xu, H., Schmidt, R., Hamm, C. A., Schobert, I. T., He, Y., Böning, G., Jonczyk, M., Hamm, B., Gebauer, B., & Savic, L. J. (2021). Comparison of intrahepatic progression patterns of hepatocellular carcinoma and colorectal liver metastases following CT-guided high dose-rate brachytherapy. Ther Adv Med Oncol., 13, 17588359211042304. https://doi.org/10.1177/17588359211042304

The following text describes the already published results in detail.

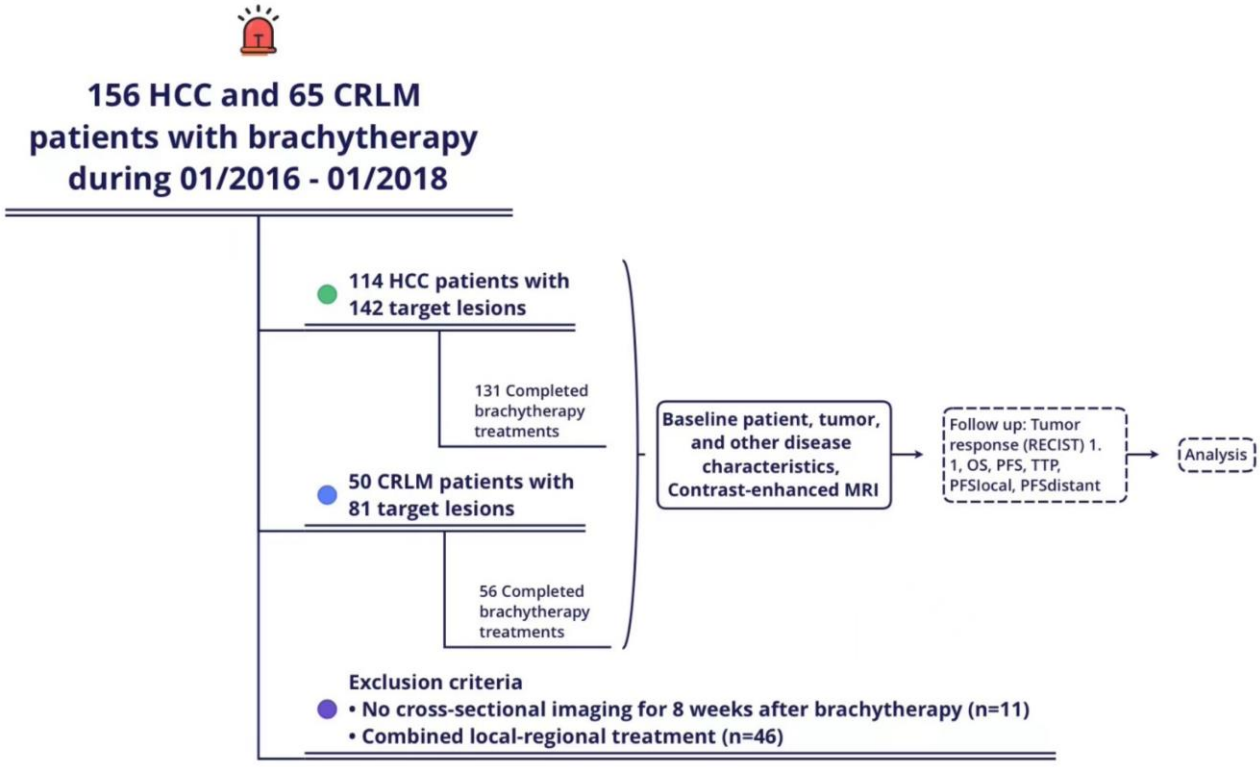

Figure 1. Study workflow and exclusion criteria.

3.1 Baseline characteristics of patients

A total of 156 HCC patients with 233 target tumors and 65 CRLM patients with 117 target tumors who received brachytherapy were identified from January 2016 to January 2018. Eleven patients who had no follow-up imaging results within 8 weeks after brachytherapy and 46 patients who had prior combined locoregional treatments of target lesions [30 patients had transarterial chemoembolization (TACE) and 16 patients had selective internal radiotherapies (SIRT)] were excluded from the study cohort. As a result, the study

population used for the study consisted of 164 patients with 223 target lesions in total, including 114 HCC patients with 142 target lesions and 50 CRLM patients with 81 target lesions, respectively. Of these 164 patients, 17 (14.9%) HCC and 6 (12.0%) CRLM patients received multiple completed brachytherapy treatments, which were considered separately in the calculation of TTP. Thus, a total of 131 and 56 completed brachytherapy treatments were performed in HCC and CRLM patients, respectively (Figure 1). Patient demographics and tumor characteristics are summarized in Table 1. The mean age of HCC and CRLM patients was 69.97 ± 10.75 and 66.30 ± 12.63 years, respectively. 97 patients with HCC had a single lesion and 17 had multiple lesions (1.24±0.50), 44 patients with CRLM had a single lesion and 6 had multiple lesions (1.62±1.00), respectively. And the target lesion diameter was 36.78±23.00 mm for HCC and 40.00±24.07 mm for CRLM.

In addition, major treatment-related adverse events (grade ⩾3 according to the Common Terminology Criteria for Adverse Events v5.1) were found to be rare in the postoperative follow-up of all patients. The incidence of adverse events was less than 1%. As a result, only two hemorrhagic events occurred in patients with hypervascularized HCC lesions, and no adverse events were observed in CRLM patients.

Table 1. Baseline patient, tumor, and other disease characteristics. This research was originally published in the journal of Therapeutic Advances in Medical Oncology. Xu, H., Schmidt, R., Hamm, C. A., Schobert, I. T., He, Y., Böning, G., Jonczyk, M., Hamm, B., Gebauer, B., & Savic, L. J. (2021). Comparison of intrahepatic progression patterns of hepatocellular carcinoma and colorectal liver metastases following CT-guided high dose-rate brachytherapy. Ther Adv Med Oncol., 13, 17588359211042304.

This table was adapted from the publication mentioned above.

Demographics	HCC	CRLM
Patient characteristics		
Number of patients	114	50
Age (years), mean ± SD	69.97±10.75	66.30±12.63
Male/female, n (%)	90/24 (78.9%/22.1%)	36/14 (72.0%/28.0%)
Target tumor characteristics		
Unifocal/multifocal, n (%)	97/17 (85.09%/14.91%)	44/6 (84.0%/12.0%)

Tumor diameter, mean ± SD (mm)	36.78±23.00	40.00±24.07
Laboratory parameters of liver function, mean ± SD		
ALT (U/l)	41.51±26.28	27.79±11.45
gamma-GT (U/l)	184.61±173.57	150.60±184.40
Bilirubin (mg/dl)	0.76±0.47	0.56±0.30
AP (second)	36.53±5.62	34.25±3.72
Previous treatments of non-target liver metastases (CRLM only), n (%)		
Non-previous treatments		8 (16.0%)
Resection		20 (40.0%)
TACE		11 (22.0%)
Resection and TACE		11 (22.0%)
Other disease characteristics (HCC only), n (%)		
Cirrhosis	47 (40.5%)	
Etiology of cirrhosis		
Hepatitis B	8 (17.0%)	
Hepatitis C	13 (27.7%)	
Alcoholic steatohepatitis	12 (25.5%)	
Nonalcoholic steatohepatitis	13 (27.7%)	
Unknown	1 (2.1%)	
Child–Pugh class		
A	39 (83.0%)	
B	8 (17.0%)	
Barcelona Clinic Liver Cancer stage		
A	45 (38.4%)	
B	60 (50.0%)	
C	10 (11.6%)	

3.2 Tumor response

A total of 114 HCC patients enrolled in this study received an average of 3.11 ± 1.80 imaging follow-up scans, and 50 CRLM patients received 2.36 ± 1.64 scans. When an event (progression, death) was detected or until they were censored, or until the end of follow-up. Tumor response assessment results according to RECIST 1.1, obtained from cross-sectional images at 8 weeks and 3 months after completion of brachytherapy, are shown in Table 2. Follow-up imaging at 8 weeks was available for each complete

treatment. However, follow-up imaging at 3 months was only available for 105 HCC and 30 CRLM cases due to progression, death, or loss of contact. As a result, no patients had a complete response (CR) in 8 weeks and 3 months follow-up. More than 70% of HCC patients had a partial response (PR) or stable disease (SD) in 8 weeks and 3 months. 21 HCC patients in 8 weeks and 29 in 3 months had progressive disease (PD) in follow-up images. For CRLM patients, two-thirds of them had a PR or SD in 8 weeks but one-third had one in 3 months.[19] CRLM patients in 8 weeks and 19 in 3 months had PD in follow-up images.

Table 2. Tumor response after brachytherapy according to the response evaluation criteria in solid tumors (RECIST) 1.1. This research was originally published in the journal of Therapeutic Advances in Medical Oncology. Xu, H., Schmidt, R., Hamm, C. A., Schobert, I. T., He, Y., Böning, G., Jonczyk, M., Hamm, B., Gebauer, B., & Savic, L. J. (2021). Comparison of intrahepatic progression patterns of hepatocellular carcinoma and colorectal liver metastases following CT-guided high dose-rate brachytherapy. Ther Adv Med Oncol., 13, 17588359211042304.

This table was adapted from the publication mentioned above.

RECIST 1.1	8 weeks		3 months	
	HCC (n=131)	CRLM (n=56)	HCC (n=105)	CRLM (n=30)
Complete response (CR)	0	0	0	0
Partial response (PR)	10 (7.6%)	4 (7.1%)	21 (20%)	4 (13.3%)
Stable disease (SD)	100 (76.3%)	33 (58.9%)	55 (52.3%)	7 (23.3%)
Progressive disease (PD)	21 (16.1%)	19 (34%)	29 (27.7%)	19 (63.4%)

Figure 2. Patterns of intrahepatic progression following brachytherapy. This research was originally published in the journal of Therapeutic Advances in Medical Oncology. Xu, H., Schmidt, R., Hamm, C. A., Schobert, I. T., He, Y., Böning, G., Jonczyk, M., Hamm, B., Gebauer, B., & Savic, L. J. (2021). Comparison of intrahepatic progression patterns of hepatocellular carcinoma and colorectal liver metastases following CT-guided high dose-rate brachytherapy. Ther Adv Med Oncol., 13, 17588359211042304.

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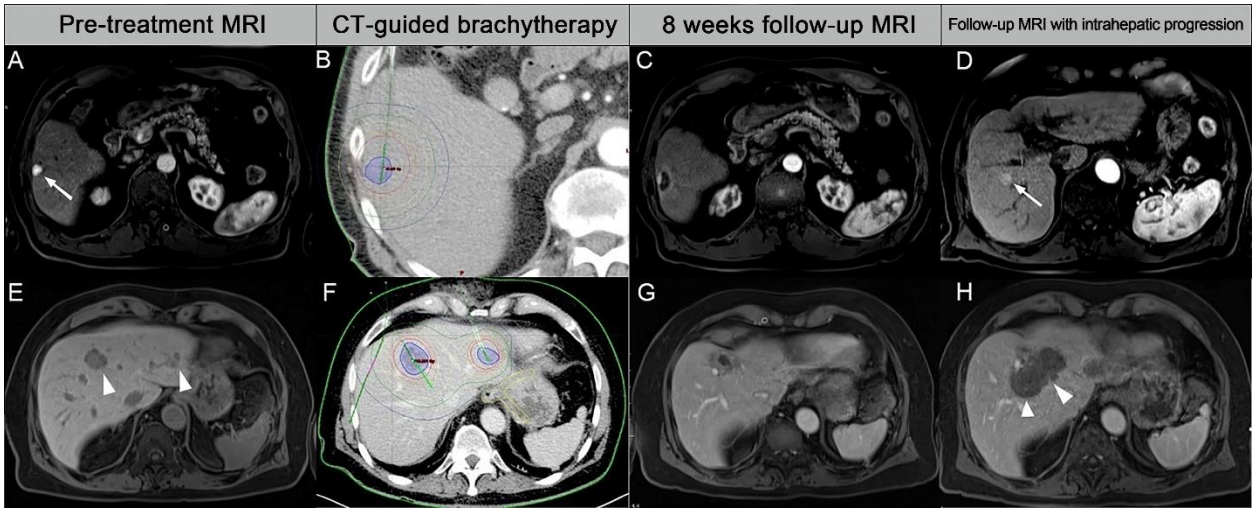

Figure 2. (A, E) show representative axial MRI scans of an exemplary HCC (arterial phase) (A) and two CRLM (venous phase) (E) prior to treatment with brachytherapy. The patient shown in the upper row had a total of three HCC lesions that were treated with brachytherapy, one of which is displayed on the images (A–C). (B, F) show the brachytherapy planning on the peri-interventional CT scan. (c, g) show the first follow-up MRI approximately 8 weeks after brachytherapy. (D) and (H) show the first type of intrahepatic progression that was detected in these patients. The white arrow in (D) indicates a distant intrahepatic HCC lesion 11.1 months after brachytherapy. The arrowheads in (H) indicate the local recurrence of the CRLM at the margin of the treated lesion 12.9 months after brachytherapy.

All results of OS, PFS, and TTP data are summarized in Table 3.

3.3 Overall survival

The median follow-up time was 24.03 (2.03-48.3) months for HCC and 13.80 (2.01-47.20) months for CRLM. During the follow-up period, 23 patients with HCC and 9 patients with CRLM had died, and 32 patients with HCC and 7 patients with CRLM were still alive at the end of the follow-up period without any events (progression or death). As for OS, no traceable death information that 91 HCC and 41 CRLM patients were censored. Almost 80% of HCC patients censored that the median survival was not reached for HCC patients. While for CRLM patients, the median OS was 47.20 months ($p = 0.279$). the OS rate was 92.9% at 6 months, 79.8% at 12 months, and 50.0% at 24 months for HCC patients. the OS rate was 78.0% at 6 months, 50.0% at 12 months, and 10.0% at 24 months in CRLM patients.

3.4 Overall and subtypes of PFS

The median overall PFS was longer in HCC [11.30 (1.33-35.37) months] than in CRLM patients [8.03 (0.73-19.80) months; $p = 0.048$] (Figure 3, A). Notably, the local recurrence of progression-free survival (PFS_{local}) was apparently longer in HCC [36.83 (1.33-40.27) months] than in CRLM patients [12.43 (0.73-21.90) months; $p = 0.001$] and with statistical significance (Figure 3, B). However, the distant intrahepatic progression ($PFS_{distant}$) was longer in CRLM patients [19.80 (1.43-19.80) months] than in HCC patients [13.50 (1.33-27.80) months; $p = 0.456$], but without statistical significance (Figures 3, C). In addition, extrahepatic metastases occurred in 7 HCC (6.1%) and 6 CRLM (12.0%) patients.

3.5 Overall and subtypes of TTP

The median TTP was longer in HCC patients [11.17 (1.60- 35.67) months] than in CRLM patients [5.27 (0.73-19.80) months; $p = 0.007$]. Notably, TTP_{local} was found to be much longer in HCC [50.13 (1.33-50.13) months] than in CRLM patients [9.90 (0.73-19.30) months; $p < 0.001$]. However, the $TTP_{distant}$ was longer in CRLM [19.80 (1.43-

19.80) months] than in HCC patients [13.50 (1.33-33.23) months; p = 0.535], but without statistical significance.

Figure 3. Overall PFS, PFS_{local}, and $PFS_{distant}$ in HCC and CRLM after brachytherapy. This research was originally published in the journal of Therapeutic Advances in Medical Oncology. Xu, H., Schmidt, R., Hamm, C. A., Schobert, I. T., He, Y., Böning, G., Jonczyk, M., Hamm, B., Gebauer, B., & Savic, L. J. (2021). Comparison of intrahepatic progression patterns of hepatocellular carcinoma and colorectal liver metastases following CT-guided high dose-rate brachytherapy. Ther Adv Med Oncol., 13, 17588359211042304.

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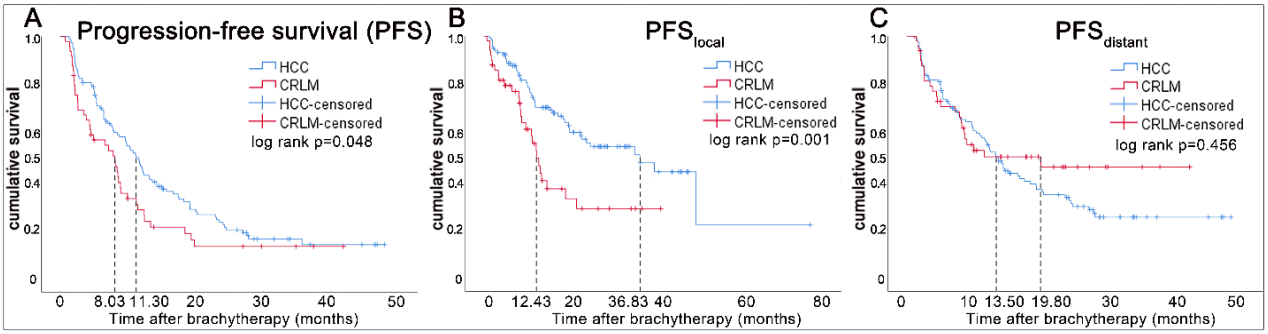

Figure 3. A. HCC patients had a longer median overall PFS (11.30 months) than CRLM (8.03 months) (p = 0.048). B. CRLM patients experienced local recurrence of the target lesions much earlier than HCC patients (36.83 months; p = 0.001). Although distant intrahepatic progression occurred earlier in HCC patients (13.50 months) than in CRLM patients (19.80 months; p = 0.456), there was no statistical significance.

Table 3. Survival data for patients with hepatocellular carcinoma (HCC) and colorectal cancer liver metastases (CRLM) undergoing CT-guided brachytherapy. This research was originally published in the journal of Therapeutic Advances in Medical Oncology. Xu, H., Schmidt, R., Hamm, C. A., Schobert, I. T., He, Y., Böning, G., Jonczyk, M., Hamm, B., Gebauer, B., & Savic, L. J. (2021). Comparison of intrahepatic progression patterns of hepatocellular carcinoma and colorectal liver metastases following CT-guided high dose-rate brachytherapy. Ther Adv Med Oncol., 13, 17588359211042304.

This table was adapted from the publication mentioned above.

	Survival data (months)	HCC	CRLM	p-value
OS	Median	N/A	47.20	0.279
	Range	2.03-48.30	2.01-47.20	
PFS	Median	11.30	8.03	**0.048**
	Range	1.33-35.37	0.73-19.80	
PFS_{local}	Median	36.83	12.43	**0.001**
	Range	1.33-40.27	0.73-21.90	
$PFS_{distant}$	Median	13.50	19.80	0.456
	Range	1.33-27.80	1.43-19.80	
TTP	Median	11.17	5.27	**0.007**
	Range	1.60-35.67	0.73-19.80	
TTPlocal	Median	50.13	9.90	**<0.001**
	Range	1.33-50.13	0.73-19.30	
$TTP_{distant}$	Median	13.50	19.80	0.535
	Range	1.33-33.23	1.43-19.80	

3.6 Predictors of PFS after brachytherapy

In the entire study cohort, the univariate Cox regression model revealed that overall PFS was significantly reduced in patients with older age [confidence interval (CI), 1.005-1.041; hazard ratio (HR), 1.023; p = 0.013], larger tumor diameter (CI, 1.008-1.021; HR, 1.015; p = 0.001), or CRLM compared with HCC (CI, 0.497-1.032; HR, 0.711; p = 0.073). In contrast, the effects of patient gender (CI, 0.560-1.272; HR, 0.843; p = 0.416) and the number of target tumors in the liver (CI, 0.504-1.080; HR, 0.738; p = 0.118) did not have a statistically significant effect on the decrease in PFS. The multivariate Cox regression model confirmed the results of the univariate Cox regression model and indicated that overall PFS was significantly lower in older patients (CI, 1.016-1.054; HR, 1.035; p = 0.001) or CRLM compared to HCC (CI; 0.368-0.874; HR, 0.567; p = 0.01), which was also compatible with the results of Kaplan-Meier analysis. Furthermore, PFS_{local} was significantly reduced in patients with older age (CI, 0.999-1.052; HR, 1.026;

p = 0.056), larger target tumor diameter (CI, 1.033-1.023; HR, 1.013; p = 0.014), and especially with CRLM (CI, 1.202-3.095; HR, 1.929; p = 0.006), respectively. The multivariate Cox regression result also confirmed the predictive value of patient age (CI, 1.001-1.053; HR, 1.026; p = 0.044) for PFS_{local}; it also showed a strong trend for target tumor diameter (CI, 1.000-1.020; HR, 1.010; p = 0.057) and CRLM (CI, 0.963-3.254; HR, 1.770; p = 0.066), respectively. In contrast, the only independent predictor of shortened $PFS_{distant}$ was patient age (CI, 1.008-1.048; HR, 1.028; p = 0.050), while the other predictors did not appear to significantly affect $PFS_{distant}$, which in accordance with Kaplan-Meier analysis (Table 4).

Table 4. Univariate and multivariate Cox regression hazard models for progression-free survival. This research was originally published in the journal of Therapeutic Advances in Medical Oncology. Xu, H., Schmidt, R., Hamm, C. A., Schobert, I. T., He, Y., Böning, G., Jonczyk, M., Hamm, B., Gebauer, B., & Savic, L. J. (2021). Comparison of intrahepatic progression patterns of hepatocellular carcinoma and colorectal liver metastases following CT-guided high dose-rate brachytherapy. Ther Adv Med Oncol., 13, 17588359211042304.

This table was adapted from the publication mentioned above.

	PFS			**PFS_{local}**			**$PFS_{distant}$**		
	95% CI for Exp(B)	HR	p-value	95% CI for Exp(B)	HR	p-value	95% CI for Exp(B)	HR	p-value
Univariate analysis									
Age	1.005-1.041	1.023	**0.013**	0.999-1.052	1.026	**0.056**	1.008-1.048	1.028	**0.050**
Gender	0.560-1.272	0.843	0.416	0.571-1.926	1.049	0.877	0.569-2.290	1.141	0.506
Target tumor diameter	1.008-1.021	1.015	**0.001**	1.033-1.023	1.013	**0.014**	0.996-1.012	1.004	0.306
Number of target lesions	0.504-1.080	0.738	0.118	0.686-2.052	1.187	0.54	0.601-1.194	0.847	0.342

Type of tumor	0.497-1.032	0.711	**0.073**	1.202-3.095	1.929	**0.006**	0.514-1.282	0.812	0.371
Multivariate analysis									
Age	1.016-1.054	1.035	**0.001**	1.001-1.053	1.026	**0.044**			
Target tumor diameter	0.998-1.014	1.006	0.117	1.000-1.020	1.010	0.057			
Type of tumor	0.368-0.874	0.567	**0.010**	0.963-3.254	1.770	0.066			

4. Discussion

4.1 Short summary of results

The key findings of this analysis were that brachytherapy achieved better local tumor control in HCC than CRLM suggesting a risk of earlier local recurrence in CRLM as compared to HCC. However, HCC patients developed distant intrahepatic progression earlier than CRLM patients and occurrence of new HCC lesions usually preceded local tumor progression of the target lesion in after brachytherapy.

4.2 Interpretation of results

In terms of overall PFS for HCC patients is 11.30 (1.33-35.37) months and for CRLM patients is 8.03 (0.73- 19.80); p = 0.048]. Especially the local tumor recurrence for HCC patients is 36.83 (1.33-40.27) compare to CRLM patients' 12.43 (0.73-21.90) months; p = 0.001. On the contrary, distant intrahepatic progression occurred earlier in HCC patients than in CRLM patients [HCC: 13.50 (1.33-27.80) months; CRLM: 19.80 (1.43-19.80) months; p = 0.456], but statistical significance was not reached. For all types of intrahepatic progression, the tumor type and patient age were the independent risk factors.

4.3 Embedding the results into the current state of research

Patients with unresectable HCC or metastatic lesions may benefit from local ablation techniques, which are accepted by the guidelines and are characterized by the ability to cause maximum control to the tumor without damaging the organs. 23-25 In the front-line clinical treatment process, microwave ablation (MWA) or radiofrequency ablation (RFA) are recommended as the first-line treatment for very early-stage disease (BCLC 0, tumors larger than 2 cm in diameter), and Although RFA is similar to liver resection and has achieved comparable tumor control, it has some limitations, such as an optimal tumor size of no more than 3-3.5 cm, heat sink effects near large blood vessels, and the potential risk for injuring adjacent bile ducts. Percutaneous ethanol injection (PEI) has the advantage of being safe and is particularly suitable for high-risk sites such as cancer foci close to the hilum, gallbladder, and gastrointestinal tissues, but requires multiple, multi-

point punctures to achieve a diffusive effect of the drug within the tumor. PEI is effective in ablating hepatocellular carcinoma ⩽2 cm in diameter, and its long-term efficacy is similar to that of RFA, but the local recurrence rate of tumors >2 cm is higher than that of RFA. [7] As an alternative to thermal ablation, brachytherapy, which is considered an alternative to other ablations by the European Society of Medical Oncology, has almost no limits on the size of the tumor that can be treated, and its therapeutic effect is not compromised by heat dissipation, and it can also be used to treat tumors near thermosensitive structures.[17, 23, 24] The benefits of brachytherapy have been demonstrated in prior research trials, resulting in a good tumor control rates at 1 year with tumors ⩽12 cm in diameter in single-institution studies with high safety profiles.[17, 25] Given that CT guiding allows the catheter to be inserted directly into the tumor, the therapeutic effect of brachytherapy is not as susceptible to patient movement or respiratory motion as conventional external beam radiotherapy and stereotactic body radiotherapy (SBRT).[15, 17] In addition, regarding the consideration of effective radiation dose, conventional external radiotherapy for HCC is limited by the surrounding tissue structures such as skin, cirrhotic liver tissue, and less sensitive hepatocellular carcinoma cells, and highly radiosensitive organs around the liver.[24] A retrospective study on brachytherapy for unresectable hepatocellular carcinoma included 98 patients with 212 HCC with a mean tumor diameter of 5 cm (range, 1.8-12.0 cm). 18 of 212 (8.5%) tumors had local recurrence, and 67 patients (68.4%) had distant intrahepatic progression. With a median PFS of 15.2 months, a median OS of 29.2 months, and 1-, 2-, and 3-year survival rates of 80, 62, and 46% respectively.[25] Additionally, for patients with a Cancer of the Liver Italian Program (CLIP) score of 2, a prospective phase II study of HCC demonstrated a significant survival benefit compared with best supportive care, resulting in median clinical survival of 23 months for those who received brachytherapy compared to 5 months for those in the control group. While patients with a CLIP score ⩾ 3 showed a median OS of 18 and 4 months, respectively.18 In a study evaluating brachytherapy for the treatment of HCC as a link to liver transplantation, results showed no differences between TACE and brachytherapy in terms of necrosis and progression-free survival after liver transplantation.[24, 25] For the HCC patients with tumor size up to 5 cm, multi-points and

multiple times ablation or combination with TACE to reduce the risk of local recurrence.[26, 27]

Other studies have concluded that in patients with intermediate-stage and large size HCCs (>5cm), the combination of TACE and ablation was the most effective treatment and also reduced liver function damage as compared to ablation alone.[28] Brachytherapy has been shown to be superior to thermal ablation alone or combined with TACE in treating tumors larger than 3-5 cm, and the recurrence rate of these tumors is relatively high.[17, 26, 27] It has been reported that brachytherapy combined with conventional TACE treatment led to a promising median OS of 28.9 and TTP of 11.7 months in patients with large (> 5 cm) and multifocal unresectable HCC.[27] Especially for multifocal HCC patients, the shrinkage of non-targeted tumors is also a major advantage for b due to the abscopal effect. As a result in our study, the distant intrahepatic progression was [PFS: 13.50 (1.33-27.80); TTP: 13.50 (1.33- 33.23) months] which occurred early than local recurrence of HCC [PFS: 36.83 (1.33-40.27); TTP: 50.13 (1.33- 50.13) months]. From a pathologist's point of view, patients with HCC may have a multicentric occurrence due to the overall pro-inflammatory tumorigenic environment of the liver under the effect of chronic inflammation, indicating the demand to develop immunotherapeutic interventions by innovations in anticancer strategies to lower the barrier of immunosuppression and restore the immune system's protection against tumor cells.[29, 30]

However, these systemic immunotherapies do not provide significant survival benefits for HCC, as more than a decade has passed without significant improvements over standard sorafenib treatment.[31] Immune checkpoint inhibitor therapy is widely used in the treatment of various solid tumors, and the efficiency of a single immune checkpoint inhibitor is low. The results of several clinical studies have confirmed that anti-angiogenic therapy can improve the microenvironment of tumors and enhance the anti-tumor sensitivity of PD-1/PD-L1 inhibitors, and anti-angiogenic combined with immunotherapy can achieve synergistic anti-tumor effects. Two-phase III studies (IMBrave150, 0RIENT32) have been successful in the first-line treatment of advanced hepatocellular carcinoma with immune checkpoint inhibitors in combination with large-molecule antiangiogenic agents (bevacizumab or biosimilars), resulting in a superior effect to sorafenib in the first-line treatment of advanced HCC and was able to prolong PFS and OS;[32] clinical studies are ongoing with small-molecule antiangiogenic agents. These studies include and are not

limited to the Phase III clinical study of camrelizumab in combination with apatinib (SHR-1210-III-310), the Phase III clinical study of lenvatinib in combination with pembrolizumab (LEAP 002), the Phase I clinical study of lenvatinib in combination with nivolumab (Study 117), the Phase III clinical study of CS1003 (PD-1 monoclonal antibody) in combination with lenvatinib (CS1003-305) and toripalimab in combination with lenvatinib Phase III clinical study. In addition, clinical studies of immune checkpoint inhibitors in combination with other drugs are also underway, such as phase III clinical studies of camrelizumab in combination with oxaliplatin-based systemic chemotherapy, phase III clinical studies of durvalumab in combination with tremelimumab (HIMALAYA), and phase III clinical studies of sintilimab in combination with IBI310 (anti-CTLA-4 monoclonal antibody). However, the overall response rate in the IMbrave 150 study did not exceed 20% and 27% after RECIST and modified RECIST, respectively, calling for other strategies to improve tumor response.[33] Strategies involving locoregional therapies could address this unmet clinical need by converting immuno-resistant tumor habitats into more susceptible tumor microenvironments that can then be targeted with immunotherapies to improve tumor response.[34] Local ablation can be used for this purpose based on a number of synergistic mechanisms. Through tissue destruction, it is proposed that the beneficial effects of increased exposure to tumor-associated antigens can be exploited.[14, 35] The use of irradiation in brachytherapy has also been shown to be effective in reprogramming the tumor stroma and microenvironment against mechanisms of cancer immune evasion to make the irradiated and necrotic tumor into an in situ vaccine that activates both innate and adaptive immunity.[36, 37]

For CRLM, complete surgical resection of liver metastases still remains the best way to treat colorectal cancer liver metastases with a potential curative intent.[38-44] Therefore, all eligible patients should receive surgical treatment at an appropriate time. Some patients whose initial liver metastases cannot be resected should also receive surgery when they are transformed into resectable lesions after neo-adjuvant treatment. Retrospective studies have shown 5-year survival rates ranging from 25% to 47%.[41, 42] As for ablation techniques, radiofrequency ablation is easy to use and safe and has demonstrated high efficacy in destroying tumor cells of liver metastases. [45-47] For patients with advanced CRLM, who consistently fail to achieve no evidence of disease status, available data suggest that the survival rate of liver metastases treated with radiofrequency ablation alone is only slightly higher than that of other non-surgical treatments.[48-51] It is currently

used only as a treatment option after ineffective chemotherapy or for recurrence of liver metastases after surgery. It is recommended to select liver metastases with a maximum diameter of <3 cm [52] and apply a maximum of five lesionss at a time.[53] However, combination approaches are commonly used where parts of the larger liver metastases can be removed first, and radiofrequency ablation can be performed for the remaining metastases <3 cm in diameter to spare liver parenchyma. Additionally, for patients with resectable CRLM, whose general condition is not suitable or who are not willing to undergo surgery, radiofrequency ablation treatment can also be considered, but care should be taken to avoid extrahepatic thermal injury, needle tunnel metastasis, infection, and incomplete ablation.[26, 54]

A retrospective cohort of recent studies compared thermal ablation to surgery alone with comparable survival rates, a decrease in perioperative morbidity and mortality, a shorter stay in the hospital, and a lower cumulative cost.[55-59] The results of the multi-center, prospective, randomized phase III trial COLLISION (clinicaltrials.gov: NCT03088150) are being awaited, which tests the hypothesis that ablation is non-inferior to surgical resection for a large cohort of patients with small (≤3 cm) CRLMs. Because the tolerated dose of whole liver radiation is much lower than the lethal dose required by tumor cells, conventional radiation therapy is only palliative in the treatment of large or multiple liver metastases. The average safe irradiation dose to the whole liver in the absence of cirrhosis is 30 Gy.[60] While this dose can significantly reduce pain or jaundice in the treatment of liver metastases invading central hilar structures, it has not been shown to prolong survival.[61, 62] Local doses targeting metastases can be increased to 60-70 Gy using hyper-segmentation or limiting the volume of the liver irradiated. [63, 64] Such higher doses may also achieve a high local control rate (>80% at 12 months). [65-67] Techniques that can be applied include 3-dimensional conformal radiotherapy (3‑D CRT), stereotactic radiotherapy (SBRT), and intensity-modulated radiotherapy (IMRT), and the use of image-guided techniques can make radiation therapy more precise and thus reduce the adverse effects on normal tissues.

Patients with unresectable large CRLM (3-5 cm) are being evaluated in the COLLISION XL trial (clinicaltrials.gov: NCT04081168), which compares SBRT and thermal ablation with a 1-year PFS endpoint. In approximately 80% of cases, insufficient liver function or multifactorial characteristics make patients ineligible for curative resection. Even with

adjuvant systemic chemotherapy, around 65% of patients develop intrahepatic recurrence within three years.[68] On the other hand, image-guided ablation techniques may be suitable remedies for older, vulnerable CRLM patients.[69] Thermal ablation is typically reserved for patients with small (＜3 cm), solitary unresectable liver metastases with comorbid conditions, or with poor performance status. The results of a recent prospective randomized trial have demonstrated that local ablation could improve OS among patients with unresectable CRLM. In particular, RFA (±surgical resection) and chemotherapy significantly extended the OS over an eight-year period, by 35.9% and 8.9%, respectively.[11] Conclusions from these studies might supposeedly partially apply to brachytherapy as well.

Regarding brachytherapy for CRLM patients, within a median follow-up of 16.9 months, a retrospective study of 80 patients with 179 unresectable CRLM (8-107 mm diameter) reported 23 (12.9%) local recurrences and 50 (62.5%) systemic progressions. As a result, the median OS was 18 months, and the time to local recurrence was 6 months.[25] In our study, the median target tumor diameter of CRLM was 40.00 ± 24.07 mm, while the median time to local recurrence was 12.43 (0.73-21.90) months, which was significantly shorter than that of HCC [36.83 (1.33-40.27); p = 0.001]. According to pathology reports, CRLMs are usually more active in peripheral tumor cell growth and have abundant blood supply, while both primary and metachronous HCC foci exhibit predominantly arterial neovascularization.[19] This suggests that incomplete ablation of the tumor margins in CRLM may cause local tumor residuals and recurrent tumor growth. Subcapsular and peritumoral enhancement may also be observed on MRI in CRLM.[70] One study showed that combined irinotecan chemoembolization and CT -guided brachytherapy can provide a more effective and safer treatment than brachytherapy alone in patients with unresectable CRLM. They observed median OS, PFS, and TTP of 8, 4, and 6 months, respectively, in patients with CRLM.[71] However, the approach needs validation in a randomized controlled trial.

Generally, cancer patients typically receive a multidisciplinary treatment plan with several, combined or sequential therapeutic approaches based on their individual stage of disease and disease characteristics including molecular pathology or mutational burden. Consequently, in this study, no standard or specific treatment was provided to all patients during the study follow-up. As this reflect clinical reality, we did not censor patients when

they received additional therapies (e.g., systemic therapies), unless they were specifically directed at the original target lesions treated with brachytherapy in this study. However, it should be noted that systemic therapies were paused at least two weeks before brachytherapy and resumed two weeks after treatment.

4.4 Strengths and weaknesses of the study

The strengths of this study are the consecutive inclusion of patients treated with brachytherapy within 2 years and the large study cohort. The baseline characteristics of patients are complete and have been included as complementary predictors to the survival analysis. In this regard, the combination of survival analysis and Cox proportional hazard regression model provides a comprehensive prediction model to analyze a potentially heterogenous cohort of patients.

This study has several limitations. Because of the retrospective analysis design, some clinical data (e.g., primary performance scores) could not be reported for all patients. In addition, pathological diagnosis of HCC and CRLM patients were not available. However, commonly used diagnostic criteria for MRI were applied to allow for noninvasive diagnosis in patients with HCC and CRLM, as recommended in the practice guidelines.[28, 70] Additionally, CRLM patients oftentimes had received pathological analysis and diagnosis of their primary disease. On follow-up imaging, RECIST 1.1 was used to assess tumor responses. The table 2 shows the tumor response of HCC/CRLM after brachytherapy as assessed by RECIST 1.1 on cross-sectional 3D imaging at 8 weeks and 3 months after each completed brachytherapy. Eight-week imaging was available for all patients and every completed treatment. However, diagnostic imaging tests were followed for 3 months in only 107 HCC and 32 CRLM patients treated for progress, death, or loss of contact. It must be emphasized that RECIST 1.1 likely does not adequately imply a tumor response to brachytherapy because the detectable response to brachytherapy (and other ablation therapies) on MRI is rather local gradual necrosis and subsequent alterations of the tumor morphology and signal intensity, which is not reflected by RECIST 1.1. Meanwhile, tumor shrinkage as measured by RECIST 1.1. may only occur gradually and later (months) after brachytherapy. Nevertheless, since it is the most widely used criterion for solid tumors and there is no dedicated response criterion for ablation or brachytherapy in particular, we decided to use RECIST 1.1. Additionally, it reliably detects tumor

progression, such as new lesions or increases in target lesions exceeding 20%, which are not expected after brachytherapy. Finally, in HCC, the median OS was not achieved because most of the patients were still alive at the end of the follow-up. However, PFS was the primary endpoint of the study and most patients have experienced progression before death in both HCC and CRLM.

4.5 Implications for practice and future research

Local ablation therapies are widely used for both primary and secondary liver tumors. HCC is the most common primary liver malignancy while CRLM is the most common type of metastasis to the liver. However, depending on the origin, underlying disease, and intrinsic prognosis, both entities have different growth kinetics and, consequently, different clinical outcomes after local ablation. This study is a hypothesis-driven study that aims to provide statistical data on the progression patterns of HCC and CRLM and compare the data with what we observe in clinical practice. The underlying cirrhosis in > 80% of HCC is prone to multifocal tumors.[72] At the time of brachytherapy, other tumors may have already manifested in the liver but were not yet detectable on MRI (micrometastases). As only visible HCC lesions are treated with brachytherapy, growth of distant tumor manifestations may precede local recurrence of the treated target lesions, making brachytherapy a good tool for local treatment of detectable disease. Therefore, many patients have also received sequential brachytherapy treatment of the new, distant, intrahepatic HCC manifestations while the initially treated target lesions were still locally controlled. In colorectal cancer, the presence of liver metastases is generally prognostically unfavourable and often indicates a high mutational burden and aggressive tumor growth.[62] While brachytherapy can be safely used for unresectable oligometastatic disease, targeted CRLM tends to recur, which may indicate the need for additional adjuvant therapies such as TACE. Therefore, CRLM is often treated with a comprehensive therapeutic combination of locoregional therapies. Therefore, the results of this hypothesis-driven study are not entirely surprising but rather provide statistical data supporting what we have observed in our routine clinical practice and what can be explained by the disease pathology.

However, to our knowledge, the progression patterns after local ablation with brachytherapy comparing different tumor entities have not yet been described previously.

In addition, with the improvement of the treatment probability of HCC and CRLM, the initial characterization of the disease progression profile and the identification of the most beneficial treatment plan for the individual patient and disease stages are becoming increasingly challenging. Thus, in addition to highlighting brachytherapy's effectiveness and strengths in primary and secondary liver cancers, our findings may also help design disease-specific surveillance strategies for future trials and elucidate the potential benefits of combination approaches of brachytherapy with adjuvant locoregional or systemic therapies.

5. Conclusions

In conclusion, brachytherapy achieves better local tumor control and longer survival for patients with HCC compared to CRLM in terms of overall PFS and local tumor recurrence. These findings elaborate on the role of local ablation in primary and secondary liver malignancies and can help determine the most beneficial therapeutic and follow-up regimen for individual patients based on their disease entity.

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Statutory Declaration

“I, Han Xu, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic [Analyse der verschiedenen intrahepatischen Progressionsmuster bei Leberkrebs / Analysis of different intrahepatic progression patterns in liver cancer], independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; http://www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Declaration of your own contribution to the publications

Detailed description of contribution to the publication: Xu H, Schmidt R, Hamm CA, Schober IT, He Y, Böning G, Jonczyk M, Hamm B, Gebauer B, Savic LJ. Comparison of intrahepatic progression patterns of hepatocellular carcinoma and colorectal liver metastases following CT-guided high dose-rate brachytherapy. Ther Adv Med Oncol. 2021.

Contributions included:

- Review of relevant literature using PubMed and Google Scholar to study the current state of the field
- Generating the concept and design of the study with the help of advisors
- Determining the criteria for exclusion and inclusion and creating Figure 1 with the help of advisors
- Patient selection based on pre-determined criteria
- Collection of relevant clinical data from hospital's electronic medical records including baseline characteristics, laboratory values, and time of progression and death, in an Excel spreadsheet
- Reviewing MR imaging with the support of a board-certified radiologist and selecting suitable MR images for Figure 2 and to illustrate the different patterns of intrahepatic progression following brachytherapy in HCC and CRLM patients
- Selecting and performing all statistical tests, including Student's t test, analysis of variance (ANOVA), Chi-square test, Cox Proportional-Hazards Model in SPSS with the help of advisors
- Discussion of statistical findings and interpretation with the help of a statistician
- Creating Tables 1 to illustrate baseline characteristics
- Creating Tables 2 to illustrate tumor response after brachytherapy according to the response evaluation criteria in solid tumors (RECIST) 1.1
- Performing time-to-event analysis and creating Kaplan Meier curve for overall survival and time to progression
- Creating Tables 3 to illustrate survival data for patients with HCC and CRLM undergoing CT-guided brachytherapy
- Creating Tables 4 to illustrate the univariate and multivariate Cox regression hazard models for progression-free survival.

- Creating Figure 3 by SPSS to illustrate the survival data of overall PFS, PFS_{local}, and $PFS_{distant}$ in HCC and CRLM after brachytherapy
- Writing the manuscript draft and incorporating co-authors' comments and addenda
- Revising the manuscript after peer-review
- Presentation of preliminary data during laboratory meetings and at the Wissenschaftssymposium of the Department of Radiology at Charité.

_____

Signature, date and stamp of first supervising university professor / lecturer

_____

Signature of doctoral candidate

Excerpt from Journal Summary List

Journal Data Filtered By: Selected JCR Year: 2019 Selected Editions: SCIE, SSCI Selected Categories: “ONCOLOGY” Selected Category Scheme: WoS Gesamtanzahl: 244 Journale: NO.34/244 Therapeutic Advances in Medical Oncology

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI
Selected Categories: **“ONCOLOGY”** Selected Category Scheme: WoS
Gesamtanzahl: 244 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	CA-A CANCER JOURNAL FOR CLINICIANS	39,917	292.278	0.093460
2	Nature Reviews Clinical Oncology	12,384	53.276	0.035980
3	NATURE REVIEWS CANCER	52,053	53.030	0.066030
4	LANCET ONCOLOGY	53,592	33.752	0.143420
5	JOURNAL OF CLINICAL ONCOLOGY	155,297	32.956	0.261940
6	Cancer Discovery	18,093	29.497	0.069280
7	CANCER CELL	41,064	26.602	0.095430
8	JAMA Oncology	13,794	24.799	0.064650
9	ANNALS OF ONCOLOGY	45,813	18.274	0.107060
10	Molecular Cancer	15,448	15.302	0.023990
11	Journal of Thoracic Oncology	18,136	13.357	0.038200
12	JNCI-Journal of the National Cancer Institute	36,018	11.577	0.045450
13	Trends in Cancer	2,351	11.093	0.010140
14	SEMINARS IN CANCER BIOLOGY	8,310	11.090	0.011730
15	Journal of Hematology & Oncology	6,732	11.059	0.015550
16	NEURO-ONCOLOGY	12,950	10.247	0.029050
17	CLINICAL CANCER RESEARCH	85,288	10.107	0.131520
18	Journal for ImmunoTherapy of Cancer	4,557	9.913	0.016030
19	CANCER RESEARCH	135,753	9.727	0.118680
20	Liver Cancer	1,131	9.720	0.002660

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	Journal of the National Comprehensive Cancer Network	6,912	9.316	0.020020
22	CANCER TREATMENT REVIEWS	9,427	8.885	0.017800
23	Cancer Immunology Research	6,969	8.728	0.026440
24	LEUKEMIA	25,819	8.665	0.048640
25	Blood Cancer Journal	2,800	8.023	0.010400
26	ONCOGENE	66,303	7.971	0.068320
27	Clinical and Translational Medicine	1,349	7.919	0.003280
28	npj Precision Oncology	500	7.717	0.001520
29	BIOCHIMICA ET BIOPHYSICA ACTA-REVIEWS ON CANCER	5,650	7.365	0.007800
30	CANCER LETTERS	34,162	7.360	0.044450
31	EUROPEAN JOURNAL OF CANCER	32,241	7.275	0.048170
32	Gastric Cancer	5,525	7.088	0.010730
33	JOURNAL OF EXPERIMENTAL & CLINICAL CANCER RESEARCH	9,316	7.068	0.014540
34	Therapeutic Advances in Medical Oncology	1,894	6.852	0.004260
35	Molecular Oncology	6,378	6.574	0.013820
36	CANCER AND METASTASIS REVIEWS	6,247	6.400	0.005940
37	Cancers	10,442	6.126	0.018740
38	Oncogenesis	2,775	6.119	0.007750
39	STEM CELLS	20,554	6.022	0.024110
40	npj Breast Cancer	814	6.000	0.003590
41	JOURNAL OF PATHOLOGY	16,307	5.979	0.017910

Selected JCR Year: 2019; Selected Categories: "ONCOLOGY"

https://journals.sagepub.com/doi/10.1177/17588359211042304

Ther Adv Med Oncol
2021, Vol. 13: 1–14
DOI: 10.1177/17588359211042304

Comparison of intrahepatic progression patterns of hepatocellular carcinoma and colorectal liver metastases following CT-guided high dose-rate brachytherapy

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Abstract

Introduction: Given the metachronous and multifocal occurrence of hepatocellular carcinoma (HCC) and colorectal cancer metastases in the liver (CRLM), this study aimed to compare intrahepatic progression patterns after computed tomography (CT)-guided high dose-rate brachytherapy.

Patients and methods: This retrospective analysis included 164 patients (114 HCC, 50 CRLM) treated with brachytherapy between January 2016 and January 2018. Patients received multiparametric magnetic resonance imaging (MRI) before, and about 8 weeks after brachytherapy, then every 3 months for the first, and every 6 months for the following years, until progression or death. MRI scans were assessed for local or distant intrahepatic tumor progression according to RECIST 1.1 and electronic medical records were reviewed prior to therapy. The primary endpoint was progression-free survival (PFS). Specifically, local and distant intra-hepatic PFS were assessed to determine differences between the intrahepatic progression patterns of HCC and CRLM. Secondary endpoints included the identification of predictors of PFS, time to progression (TTP), and overall survival (OS). Statistics included Kaplan–Meier analysis and univariate and multivariate Cox regression modeling.

Results: PFS was longer in HCC [11.30 (1.33–35.37) months] than in CRLM patients [8.03 (0.73–19.80) months, $p = 0.048$], respectively. Specifically, local recurrence occurred later in HCC [PFS: 36.83 (1.33–40.27) months] than CRLM patients [PFS: 12.43 (0.73–21.90) months, $p = 0.001$]. In contrast, distant intrahepatic progression occurred earlier in HCC [PFS: 13.50 (1.33–27.80) months] than in CRLM patients [PFS: 19.80 (1.43–19.80) months, $p = 0.456$] but without statistical significance. Multivariate Cox regression confirmed tumor type and patient age as independent predictors for PFS.

Conclusion: Brachytherapy proved to achieve better local tumor control and overall PFS in patients with unresectable HCC as compared to those with CRLM. However, distant progression preceded local recurrence in HCC. As a result, these findings may help design disease-specific surveillance strategies and personalized treatment planning that highlights the strengths of brachytherapy. They may also help elucidate the potential benefits of combinations with other loco-regional or systemic therapies.

Keywords: ablation, brachytherapy, HCC imaging, local ablation therapy, prognostic prediction, radiation therapy

Received: 26 April 2021; revised manuscript accepted: 9 August 2021.

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Introduction

Liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide, with about 841,000 new cases and 782,000 deaths annually.[1] Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and is a major global health problem.[2,3] Besides primary liver cancer, the liver is a common site for metastases of cancers that derive from other organs such as colorectal cancer liver metastases (CRLM). In 25% of patients, CRLM occur synchronously, while up to 60% of patients will develop them during the course of the disease.[4] Despite the availability of a multidisciplinary treatment armamentarium, the 5-year survival rate for patients with CRLM remains as poor as 10%.[5]

Commonly used chemotherapeutic treatments for CRLM lead to a median life-prolonging effect of 2.3 months but bear the risk of systemic adverse events.[6] In liver-dominant disease, local, minimally-invasive therapies are effective alternatives, with a potentially reduced risk of side effects.[7] Thermal local ablation techniques lead to similar overall survival (OS) rates when compared with those for hepatic resection; however, the effect of treatment is limited by the heat-sink effect when lesions are located close to vessels or exceed a diameter of 5 cm.[8]

Additionally, substantial evidence exists in support of non-thermal ablation with computed tomography (CT)-guided interstitial high-dose rate brachytherapy, which comprises the catheter-based, percutaneous internal radiation of the tumor with a gamma-emitting iridium-192 source that is temporarily applied and removed immediately after treatment.[9] Due to precise 3D radiation planning and the rapid dose drop outside the target tissue, brachytherapy allows for the 'inside-out' application of a very high radiation dose to the target volume in a single fraction (>100 Gy in central tumor parts), while sparing surrounding liver parenchyma.[10] The overall patient safety of the intervention is very high and local tumor control rates are encouraging. As a result, it represents an important option in treating patients with advanced hepatic tumors without a surgical alternative, especially when reduced liver function due to previous surgery or chronic liver disease is present. With this in mind, brachytherapy is also applied in patients with large (>5 cm) and multifocal unresectable HCC, where it demonstrates promising median OS of 28.9 and time-to-progression (TTP) of 11.7 months.[11]

However, current monitoring strategies for patients who received brachytherapy do not consider the underlying tumor entity. Moreover, very little is known about its effect on tumor susceptibility to brachytherapy or tumor response.[12] Evidence exists supporting the theory that the majority of recurrences are limited to the liver and develop within the first year after treatment.[13,14] Although this may seem intuitively right, it has not been previously reported for HCC and CRLM in the literature and no study exists that further investigated tumor-specific profiles of intrahepatic progression.

Given the metachronous and multifocal occurrence of HCC and CRLM possibly requiring personalized monitoring and treatment strategies, this study aimed to compare progression-free survival (PFS) and specifically local and distant intrahepatic progression patterns of HCC and CRLM after brachytherapy using longitudinal multiparametric magnetic resonance imaging (MRI).

Methods

Study cohort and endpoints

This retrospective, single-institution study was compliant with the Health Insurance Portability and Accountability Act (HIPAA) and approved by the institutional review board (EA4/089/17). Informed consent was waived, given the retrospective observational study design. All patients had been discussed in a multidisciplinary tumor board and had received a recommendation for tumor ablation. Consecutive patients with HCC and CRLM who received brachytherapy between January 2016 and January 2018 were included in this study. They had received at least one baseline MRI scan within 30 days prior to, and one follow-up MRI scan about 8 weeks after brachytherapy. All target lesions were naïve to loco-regional minimally invasive liver-directed therapies.

The primary endpoint was PFS. Specifically, local and distant intra-hepatic PFS were assessed to determine differences between the intrahepatic progression patterns of HCC and CRLM as further specified below. Secondary endpoints included the identification of predictors of PFS, TTP, and OS.

CT-guided high dose-rate brachytherapy

Technical brachytherapy protocol. Procedural standards of the brachytherapy were described in

detail elsewhere.[15,16] Briefly, patients were treated under conscious sedation (midazolam and fentanyl) and local anesthesia (xylocaine). The therapies were performed by two interventional radiologists with 12 and 8 years of experience in brachytherapy, respectively. Under CT-fluoroscopic guidance, a 6F angiographic sheath was inserted into the lesion. Through this sheath, the closed-ended 6F brachytherapy catheter (Primed, Halberstadt, Germany) was introduced. The array of the catheter in relation to the tumor was depicted on a contrast-enhanced CT scan (primary slice thickness 0.625 mm, reconstructed to a slice thickness of 5 mm), which was used for further treatment planning on a 3D radiation planning workstation (Brachyvision; Varian Medical Systems, Palo Alto, CA, USA). A portal venous contrast phase (45 seconds after injection) was chosen for CRLM and an arterial phase (15 seconds after injection) for HCC.

The clinical target volume was segmented manually on these planning CT scans and the general intention was to ablate each lesion with a tumor enclosing target dose of 20 Gy using the iridium-192 source (Gammamed 12; Varian Medical Systems). Adjacent structures at risk, such as the stomach or the duodenum, were marked and their dosage was calculated; if necessary, the overall dosage was modified according to Collettini *et al.*[17] After completion of the brachytherapy, the catheter was retracted and the puncture channels were sealed with resorbable, thrombogenic material (Gelfoam; Pfizer Inc., New York, NY, USA) to avoid bleeding.

Sequential brachytherapy treatments. A brachytherapy treatment was defined completed when all target lesions were completely irradiated with the target dose of 20 Gy. Target lesions were selected, and the treatment was planned at the discretion of the interventional radiologist. Sequential treatments were performed if the patient had multifocal or large tumors at baseline, where the radiation volume had to be split into sequential sessions to avoid adverse events from tumor lysis, or to reduce cumulative puncture risk. As a result, patients were included who had received up to 4 sequential brachytherapy sessions within 4–6 week-intervals to achieve completed brachytherapy.

If the patient developed new intrahepatic lesions during follow-up that were not present at baseline and were treated with brachytherapy in a new treatment cycle (at least 8 weeks after the first brachytherapy), these additional brachytherapy's were considered separate treatments for the calculation of the TTP. However, for the calculation of the PFS, this event was considered tumor progression and follow-up was terminated.

Image acquisition and analysis

MRI protocol. MRI scans were acquired on a 1.5-T-device (Avanto, Siemens, Erlangen, Germany) using an eight-channel body phased-array coil. Hepatocyte-specific contrast agent (Primovist; Bayer, Leverkusen, Germany) was for dynamic contrast-enhanced sequences. A standard volume interpolated breath-hold examination sequence (VIBE) in the axial plane with a TR of 4.26 ms, a TE of 1.87 ms, a flip angle (FA) of 10°, a slice thickness of 3 mm, and a matrix size of 256 × 127 was acquired; this covered the entire liver with 60–72 slices and an adjusted field of view (FOV) of 255–300 × 340–400 mm. Images were evaluated with Merlin Phoenix version 5.8 (Pixmeo SARL, Bernex, Switzerland).

MRI schedule and tumor response assessment. Patients received multiparametric MRI before, and about 8 weeks after, brachytherapy, then every 3 months for the first, and every 6 months for the following years, respectively, until death or loss to follow-up.

Tumor response according to the response evaluation criteria in solid tumors (RECIST) 1.1 was assessed on the follow-up imaging datasets by two radiologists with 5 and 7 years of experience in abdominal imaging, who did not perform the brachytherapy.[18] The follow-up ended in June 2020, and all MRI or CT scans obtained until June 2020 were included in the analysis.

Kaplan–Meier survival analysis

Overall survival, progression-free survival, and time-to-progression. OS, PFS, and TTP were analyzed using Kaplan–Meier analysis and the log-rank test. OS was defined as the time between the first completed brachytherapy treatment and the date of death from any cause. Patients who were lost to follow-up or still alive at the time of the last follow-up without an event (progression or death) were censored at the respective timepoint.

PFS was defined as the time between the first completed brachytherapy treatment and death or the occurrence of intrahepatic or extrahepatic

tumor progression, respectively. Patients who received additional loco-regional treatments of the target lesions were censored at the respective timepoint. Patients without progression of any kind or death until the end of follow-up were censored at the end of follow-up.

TTP was defined as the time between any completed brachytherapy treatment and the occurrence of intrahepatic or extrahepatic tumor progression. In contrast to PFS, TTP in this study was calculated for every completed brachytherapy treatment cycle (i.e., multiple completed brachytherapy treatments on different target lesions of the same patient).

Patterns of intrahepatic progression. In addition to the overall PFS and TTP, two specific progression patterns were separately assessed for subgroup analyses. These subtypes of progression were defined as local recurrence (PFS_{local} or TTP_{local}) and distant intrahepatic progression ($PFS_{distant}$ or $TTP_{distant}$). Local recurrence was defined as an increase of the target lesion diameter >20% according to RECIST 1.1. While PFS_{local} was assessed on the target lesions treated during the first completed brachytherapy, TTP_{local} was always defined based on the target lesions treated during the respective brachytherapy cycle. Distant intrahepatic progression was defined as the occurrence of a new malignant hepatic lesion at a different site that had not been treated by brachytherapy before.

Cox regression model

In addition to the Kaplan–Meier analysis, a univariate Cox proportional hazard regression model was developed to evaluate the predictive value of each coverage factor (predictor variables). For the overall PFS, the PFS_{local} and $PFS_{distant}$, statistically significant variables ($p < 0.1$) were selected to develop a multivariate Cox proportional hazard regression model to evaluate their predictive value for the overall PFS, the PFS_{local} and $PFS_{distant}$, when taking into account multiple coverage factors. Covariates were selected, which had a previously reported effect on survival outcome.[19–22] Besides imaging-based tumor characteristics (tumor type, target lesion diameter, number of target lesions), clinical and demographic parameters (age, gender) derived from electronic medical records prior to therapy were included in the regression model.

Statistics

Descriptive statistics were reported as the mean ± standard deviation (SD) and median and range, respectively. Statistical significance was defined as $p < 0.05$. Survival and Cox regression analyses were performed using SPSS software (IBM SPSS Statistics, version 26, 2019, IBM Corp, Armonk, NY, USA).

Results

Patient characteristics

In total, 156 HCC patients with 233 target tumors and 65 CRLM patients with 117 target tumors receiving brachytherapy were identified. Eleven patients who had no cross-sectional imaging 8 weeks after brachytherapy and 46 patients with combined loco-regional treatments to the target lesions [30 transarterial chemoembolization (TACE), 16 selective internal radiotherapy (SIRT)] were excluded. As a result, the total study population considered for the analysis consisted of 164 patients with 223 target lesions including 114 HCC patients with 142 target lesions and 50 CRLM patients with 81 target lesions, respectively. Of these 164 patients, 17 (14.9%) HCC and 6 (12.0%) CRLM patients received multiple completed brachytherapy treatments that were considered separately for the calculation of the TTP. As a result, in total, 131 and 56 completed brachytherapy treatments were performed in HCC and CRLM patients, respectively (Figure 1).

The mean age was 69.97 ± 10.75 and 66.30 ± 12.63 years in HCC and CRLM patients, and 78.9% and 72.0% were men, respectively. Patients with HCC presented with 1.24 ± 0.50 lesions at baseline and patients with CRLM with 1.62 ± 1.00, respectively. The target lesion diameter was 36.78 ± 23.00 mm in HCC and 40.00 ± 24.07 mm in CRLM. Patient demographics and tumor characteristics are summarized in Table 1.

Overall, major treatment-related complications (grade ⩾3 according to the Common Terminology Criteria for Adverse Events v5.1) following brachytherapy were rare. The rate of complications was <1%: comprising two bleedings that occurred in patients with hypervascularized HCC lesions.

Tumor response

In total, the 114 HCC patients included in this study received 3.11 ± 1.80 follow-up imaging scans and the 50 CRLM patients received 2.36 ± 1.64 scans, respectively, until an event (progression, death) was noted, or until they were censored, or until the end of follow-up. Results from the tumor response assessment according to RECIST 1.1 evaluated on the cross-sectional imaging 8 weeks and 3 months after completed brachytherapy are reported in Table 2. Follow-up imaging at 8 weeks was available for every complete treatment. However, follow-up imaging at 3 months was only available in 105 HCC and 30 CRLM cases due to progression, death, or loss of contact.

Overall survival

All OS, PFS, and TTP data are summarized in Table 3.

The median follow-up time was 24.03 (2.03–48.3) months for HCC and 13.80 (2.01–47.20) months for CRLM. During the follow-up period, 23 HCC and 9 CRLM patients had died, and 32 HCC and 7 CRLM patients were still alive at the end of follow-up without an event (progression or death), respectively. As for the OS, 91 HCC and 41 CRLM patients were censored. The median survival in HCC patients was not reached. For CRLM patients, the median OS was 47.20 months ($p = 0.279$). The OS rate was 92.9% at 6 months, 79.8% at 12 months, and 50.0% at 24 months in HCC patients, respectively. The OS rate was 78.0% at 6 months, 50.0% at 12 months, and 10.0% at 24 months of CRLM patients, respectively.

Progression-free survival

The median overall PFS was longer in HCC [11.30 (1.33–35.37) months] than in CRLM patients [8.03 (0.73–19.80) months; $p = 0.048$]. In particular, the local recurrence (PFS_{local}) was longer in HCC [36.83 (1.33–40.27) months] than in CRLM patients [12.43 (0.73–21.90) months; $p = 0.001$] (Figure 2). However, the distant intrahepatic progression ($PFS_{distant}$) was longer in CRLM [19.80 (1.43–19.80) months] than in HCC patients [13.50 (1.33–27.80) months; $p = 0.456$] but without statistical significance (Figures 2 and 3). In addition, 7 HCC (6.1%) and 6 CRLM patients (12.0%) experienced extrahepatic metastases.

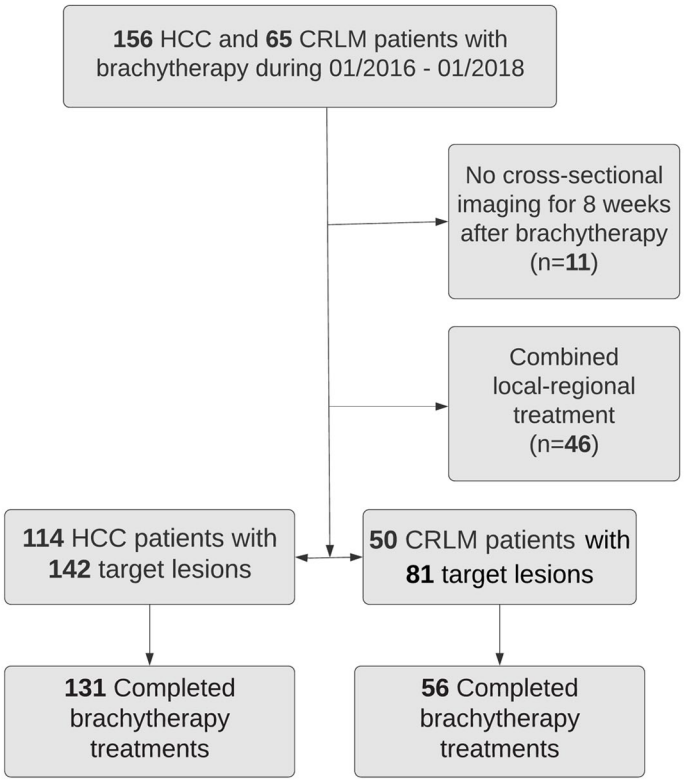

Figure 1. Study workflow and exclusion criteria.
CRLM, colorectal cancer liver metastases; HCC, hepatocellular carcinoma.

Time-to-progression

Median TTP was longer in HCC [11.17 (1.60–35.67) months] than CRLM patients [5.27 (0.73–19.80) months; $p = 0.007$]. In particular, the TTP_{local} was detected to be much longer in HCC [50.13 (1.33–50.13) months] than in CRLM patients [9.90 (0.73–19.30) months; $p < 0.001$]. However, the $TTP_{distant}$ was longer in CRLM [19.80 (1.43–19.80) months] than in HCC patients [13.50 (1.33–33.23) months; $p = 0.535$], but without statistical significance.

Predictors of progression-free survival after brachytherapy

In the entire study cohort, the univariate Cox regression model revealed that overall PFS was significantly reduced in patients with older age [confidence interval (CI), 1.005–1.041; hazard ratio (HR), 1.023; $p = 0.013$], larger tumor diameter (CI, 1.008–1.021; HR, 1.015; $p = 0.001$), or CRLM, as compared to HCC (CI, 0.497–1.032; HR, 0.711; $p = 0.073$). The multivariate Cox regression model confirmed the findings of the univariate Cox regression model and revealed that overall PFS was

Table 1. Baseline patient, tumor, and other disease characteristics.

Demographics	HCC	CRLM
Patient characteristics		
Number of patients	114	50
Age (years), mean ± SD	69.97 ± 10.75	66.30 ± 12.63
Male/female, *n* (%)	90/24 (78.9/22.1)	36/14 (72.0/28.0)
Target tumor characteristics		
Unifocal/multifocal, *n* (%)	97/17 (85.09/14.91)	44/6 (84.0/12.0)
Tumor diameter, mean ± SD (mm)	36.78 ± 23.00	40.00 ± 24.07
Laboratory parameters of liver function, mean ± SD		
ALT (U/l)	41.51 ± 26.28	27.79 ± 11.45
AST (U/l)	50.25 ± 30.33	35.46 ± 10.93
Gamma-glutamyl-transferase (U/l)	184.61 ± 173.57	150.60 ± 184.40
Bilirubin (mg/dl)	0.76 ± 0.47	0.56 ± 0.30
AP (second)	36.53 ± 5.62	34.25 ± 3.72
Previous treatments of non-target liver metastases (CRLM only), *n* (%)		
Non-previous treatments		8 (16.0)
Resection		20 (40.0)
TACE		11 (22.0)
Resection and TACE		11 (22.0)
Other disease characteristics (HCC only), *n* (%)		
Cirrhosis	47 (40.5)	
Etiology of cirrhosis n (%)		
Hepatitis B	8 (17.0)	
Hepatitis C	13 (27.7)	
Alcoholic steatohepatitis	12 (25.5)	
Nonalcoholic steatohepatitis	13 (27.7)	
Unknown	1 (2.1)	
Child–Pugh class n (%)		
A	39 (83.0)	
B	8 (17.0)	
Barcelona Clinic Liver Cancer stage n (%)		
A	45 (38.4)	
B	60 (50.0)	
C	10 (11.6)	

ALT, alanine aminotransferase; AP, alkaline phosphate; AST, aspartate aminotransferase; CRLM, colorectal cancer liver metastases; HCC, hepatocellular carcinoma; SD, standard deviation; TACE, transarterial chemoembolization.

Table 2. Tumor response after brachytherapy according to the response evaluation criteria in solid tumors (RECIST) 1.1.

RECIST 1.1	8 weeks		3 months	
	HCC ($n=131$)	CRLM ($n=56$)	HCC ($n=105$)	CRLM ($n=30$)
CR	0	0	0	0
PR	10	4	21	4
SD	100	33	55	7
PD	21	19	29	19

HCC, hepatocellular carcinoma; CRLM, colorectal cancer liver metastases; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3. Survival data for patients with hepatocellular carcinoma (HCC) and colorectal cancer liver metastases (CRLM) undergoing CT-guided brachytherapy.

	Survival data (months)	HCC	CRLM	*p*-value
OS	Median	N/A	47.20	0.279
	Range	2.03–48.30	2.01–47.20	
PFS	Median	11.30	8.03	**0.048**
	Range	1.33–35.37	0.73–19.80	
PFS_{local}	Median	36.83	12.43	**0.001**
	Range	1.33–40.27	0.73–21.90	
$PFS_{distant}$	Median	13.50	19.80	0.456
	Range	1.33–27.80	1.43–19.80	
TTP	Median	11.17	5.27	**0.007**
	Range	1.60–35.67	0.73–19.80	
TTP_{local}	Median	50.13	9.90	**<0.001**
	Range	1.33–50.13	0.73–19.30	
$TTP_{distant}$	Median	13.50	19.80	0.535
	Range	1.33–33.23	1.43–19.80	

N/A, not assessable (the median overall survival for HCC was not reached); OS, overall survival; PFS, progression-free survival; $PFS_{distant}$/$TTP_{distant}$, distant intrahepatic progression; PFS_{local}/TTP_{local}, local recurrence; TTP, time to progression; bold *p*-values indicate statistical significance in the log-rank test ($p < 0.05$).

significantly reduced in patients with older age (CI, 1.016–1.054; HR, 1.035; $p=0.001$) or CRLM, as compared to HCC (CI; 0.368–0.874; HR, 0.567; $p=0.01$), which was also consistent with the findings from the Kaplan–Meier analysis.

In addition, the PFS_{local} was significantly reduced in patients with older age (CI, 0.999–1.052; HR, 1.026; $p=0.056$), larger target tumor diameter (CI, 1.033–1.023; HR, 1.013; $p=0.014$), and particularly CRLM (CI, 1.202–3.095; HR, 1.929; $p=0.006$). The multivariate Cox regression model

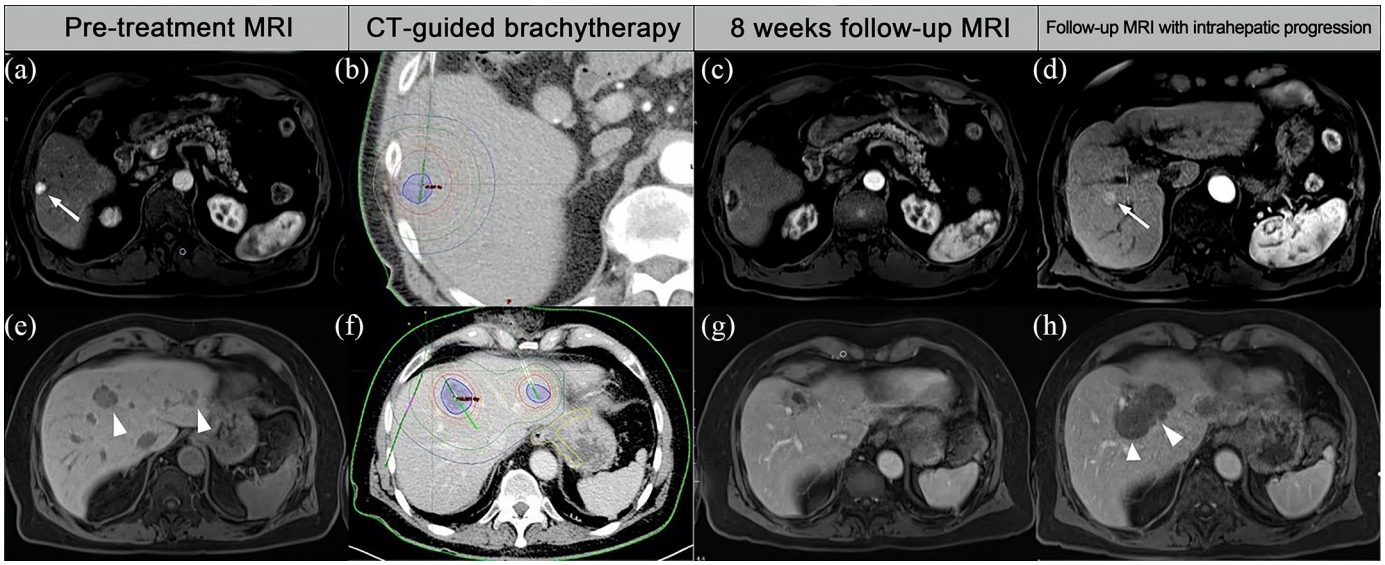

Figure 2. Patterns of intrahepatic progression following brachytherapy. (a, e) show representative axial MRI scans of an exemplary HCC (arterial phase) (a) and two CRLM (venous phase) (e) prior to treatment with brachytherapy. The patient shown in the upper row had a total of three HCC lesions that were treated with brachytherapy, one of which is displayed on the images (a–c). (b, f) show the brachytherapy planning on the peri-interventional CT scan. (c, g) show the first follow-up MRI approximately 8 weeks after brachytherapy. (d) and (h) show the first type of intrahepatic progression that was detected in these patients. The white arrow in (d) indicates a distant intrahepatic HCC lesion 11.1 months after brachytherapy. The arrowheads in (h) indicate the local recurrence of the CRLM at the margin of the treated lesion 12.9 months after brachytherapy.
CRLM, colorectal cancer liver metastases; CT, computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging

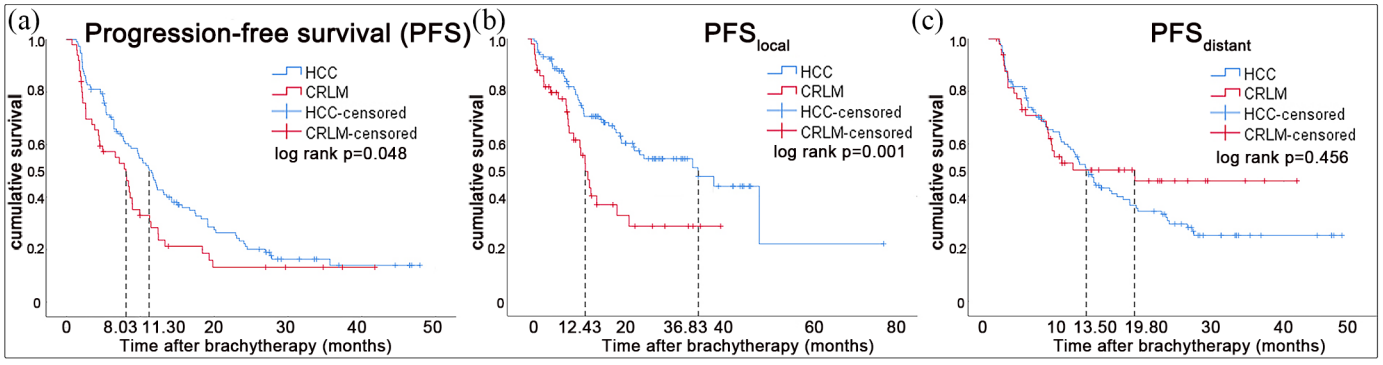

Figure 3. Overall PFS, PFS_{local}, and $PFS_{distant}$ in HCC and CRLM following brachytherapy. (a) The median overall PFS was longer in HCC (11.30 months) compared to CRLM (8.03 months) ($p = 0.048$). Local recurrence of the target lesions occurred much earlier in CRLM (12.43 months) compared to HCC (36.83 months; $p = 0.001$). However, distant intrahepatic progression occurred earlier in HCC (13.50 months) than in CRLM patients (19.80 months; $p = 0.456$), but without statistical significance.
CRLM, colorectal cancer liver metastases; HCC, hepatocellular carcinoma; PFS, progression-free survival; $PFS_{distant}$, distant intrahepatic progression; PFS_{local}, local recurrence.

confirmed the predictive value of the patients' age (CI, 1.001–1.053; HR, 1.026; $p = 0.044$) for PFS_{local}; it also revealed a strong trend for target tumor diameter (CI, 1.000–1.020; HR, 1.010; $p = 0.057$) and CRLM (CI, 0.963–3.254; HR, 1.770; $p = 0.066$), respectively.

By contrast, the only independent predictor for reduced $PFS_{distant}$ was the patients' age (CI, 1.008–1.048; HR, 1.028; $p = 0.050$), while the tumor type did not seem to have a significant effect on $PFS_{distant}$, which was consistent with the Kaplan–Meier analysis (Table 4).

Table 4. Univariate and multivariate Cox regression hazard models for progression-free survival.

	PFS			PFS_{local}			$PFS_{distant}$		
	95% CI for Exp(B)	HR	*p*-value	95% CI for Exp(B)	HR	*p*-value	95.0% CI for Exp(B)	HR	*p*-value
Univariate analysis									
Age	1.005–1.041	1.023	**0.013**	0.999–1.052	1.026	**0.056**	1.008–1.048	1.028	**0.050**
Gender	0.560–1.272	0.843	0.416	0.571–1.926	1.049	0.877	0.569–2.290	1.141	0.506
Target tumor diameter	1.008–1.021	1.015	**0.001**	1.033–1.023	1.013	**0.014**	0.996–1.012	1.004	0.306
Number of target lesions	0.504–1.080	0.738	0.118	0.686–2.052	1.187	0.54	0.601–1.194	0.847	0.342
Type of tumor	0.497–1.032	0.711	**0.073**	1.202–3.095	1.929	**0.006**	0.514–1.282	0.812	0.371
Multivariate analysis									
Age	1.016–1.054	1.035	**0.001**	1.001–1.053	1.026	**0.044**			
Target tumor diameter	0.998–1.014	1.006	0.117	1.000–1.020	1.010	0.057			
Type of tumor	0.368–0.874	0.567	**0.010**	0.963–3.254	1.770	0.066			

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; $PFS_{distant}$, distant intrahepatic progression; PFS_{local}, local recurrence; bold *p*-values indicate statistical significance in the univariate ($p < 0.1$) and multivariate analysis ($p < 0.05$).

Discussion

The main finding of this study was that brachytherapy proved to achieve better tumor control of HCC than CRLM in terms of overall PFS [HCC: 11.30 (1.33–35.37) months; CRLM: 8.03 (0.73–19.80); $p = 0.048$] and especially local tumor recurrence [HCC: 36.83 (1.33–40.27); CRLM: 12.43 (0.73–21.90); $p = 0.001$]. By contrast, distant intrahepatic progression occurred earlier in HCC than in CRLM patients [13.50 (1.33–27.80) months; CRLM: 19.80 (1.43–19.80) months; $p = 0.456$] but without statistical significance. Patient age was the only independent risk factor for all types of intrahepatic progression.

Since HCC is less likely to develop extrahepatic metastases, local ablation techniques are often applied and guideline-approved, as they cause select maximum damage to the tumor while preserving organ function.[23–25] Thermal ablation by radiofrequency (RFA) or microwave ablation (MWA) is recommended as a first-line treatment in very early-stage disease (BCLC 0, tumors < 2 cm diameter), where RFA has demonstrated similar outcomes to liver resection.[26] However, thermal ablations have several limitations, including an optimal tumor size not exceeding 3–3.5 cm, heat sink effects in the vicinity of large blood vessels, and the risk of causing injury to adjacent bile ducts. In contrast to thermal ablation, brachytherapy, which is considered an alternative to thermal ablations by the clinical practice guidelines of the European Society for Medical Oncology, has almost no restrictions with regards to the tumor size that can be treated, its therapeutic effect is not degraded by heat dissipation, and it can also be used to treat tumors in the vicinity of thermosensitive structures.[12,26,27] Brachytherapy has proven effective, with tumor control rates $>90\%$ after 12 months in tumors of $\leqslant 12$ cm diameter in single-center studies with excellent safety profiles.[12,28] Unlike conventional external beam radiotherapy and stereotactic body radiotherapy (SBRT), the therapeutic effect of brachytherapy is not endangered by patient movement or respiratory excursion since the applicator is anchored directly within the tumor.[10,12] In addition, conventional percutaneous radiation of HCC is limited by the low radiation sensitivity of hepatocellular cancer cells, altered tissue structures in cirrhotic livers, and very radioresponsive organs surrounding the liver that adversely affect the dose of radiation used to target the tumor.[27]

A retrospective study included 98 patients with 212 unresectable HCC with a mean tumor diameter of 5 cm (range, 1.8–12.0 cm). Eighteen of 212 (8.5%) tumors showed local, and 67 patients (68.4 %) experienced distant tumor progression, respectively. The median PFS was 15.2 months, and the median OS was 29.2 months with a 1-, 2-, and

3-year OS rate of 80, 62, and 46%, respectively.[28] Furthermore, a prospective phase II study of HCC showed a high survival benefit compared to best supportive care with a median OS of 23 months in the brachytherapy group *versus* 5 months in the control group for patients with a Cancer of the Liver Italian Program (CLIP) score of 2. Patients with CLIP scores ⩾ 3 demonstrated a median OS of 18 *versus* 4 months, respectively.[18] In a study evaluating brachytherapy for HCC as a bridge to liver transplant, the results showed a similar or even higher degree of necrosis and lower recurrence rates after liver transplant than TACE.[27,28]

For the treatment of large HCC up to 5 cm, ablation can be combined with TACE to decrease the risk of local recurrence.[29,30] Positive results were obtained in patients with intermediate stage and large HCCs, which became the ideal setting for the combination of TACE and ablation.[31] In this setting, the superiority of brachytherapy has been reported over thermal ablation alone, or in combination with TACE, both of which are incapable of complete treatment of tumors larger than 3–5 cm leading to relatively high rates of local recurrence.[12,29,30] Previous studies investigating brachytherapy in combination with conventional TACE demonstrated a promising median OS of 28.9 and TTP of 11.7 months in patients with large (>5 cm) and multifocal unresectable HCC.[30]

In our study, distant intrahepatic progression [PFS: 13.50 (1.33–27.80); TTP: 13.50 (1.33–33.23) months] preceded local recurrence in HCC [PFS: 36.83 (1.33–40.27); TTP: 50.13 (1.33–50.13) months]. As HCC is characterized by this multicentric occurrence and oftentimes develops in chronic liver diseases that are hypothesized to generate a pro-inflammatory tumorigenic milieu, innovations in anti-cancer strategies focus on immunotherapeutic interventions that aim at lowering the barrier of immunosuppression and restoring the resources of the immune system against cancer cells.[32,33] However, systemic approaches using such immunotherapies have largely failed to elicit meaningful survival benefits in HCC and no significant advantages have been made over standard treatment with sorafenib in more than a decade.[34] Just recently, the groundbreaking results of the IMbrave 150 trial showed that the combination of the immune checkpoint inhibitor atezolizumab with the anti-angiogenic agent bevacizumab was superior to sorafenib in the first-line treatment of advanced HCC and able to prolong PFS and OS.[35] However, overall response rates in the IMbrave 150 trial did not exceed 20% or 27%, according to RECIST and modified (m)RECIST, respectively, calling for further strategies to improve the tumor susceptibility.[36]

This unmet clinical need could be addressed by strategies that exploit loco-regional therapies as conditioning tools to convert immune-resistant tumor habitats towards a more susceptible tumor microenvironment that can then be targeted with immunotherapies even in earlier disease stages.[37] The commonly cited rationale to utilize local ablation for this purpose is based on a variety of synergistic mechanisms; it proposes to exploit the presumably favorable effects of increased tumor-associated antigen exposure through tissue destruction.[8,38] Recent data has further shown that radiation, as applied during brachytherapy, could re-program the tumor stroma and microenvironment against mechanisms of cancer immune evasion and convert the irradiated and gradually necrotic tumor into *in situ* vaccines to prime both the innate and adaptive immune system.[39,40]

In CRLM, surgical resection remains the standard of care for liver-only disease; retrospective studies have reported 5-year survival rates ranging from 25% to 47%.[41,42] Comparing surgical resection alone for resectable disease with RFA for unresectable disease, RFA demonstrated inferior survival rates but significantly fewer complications.[43] However, many observational studies were confounded by the treatment indication, because thermal ablation was solely performed for unresectable disease. The more recent retrospective cohort using matched-pair or multivariate analysis reported comparable survival rates for thermal ablation alone *versus* surgery alone, while also decreasing perioperative morbidity and mortality, length of hospitalization, and accumulative costs with superior QoL.[43–47] The results from the multicenter phase-III prospective randomized COLLISION trial (Clinicaltrial.gov identifier: NCT03088150) are awaited, which tests the hypothesis of non-inferiority of ablation compared to surgical resection in a large cohort of patients with small (⩽3 cm) CRLM. Additionally, the ongoing COLLISION XL trial (Clinicaltrial.gov identifier: NCT04081168) will compare SBRT and thermal ablation in patients with unresectable large CRLM (3–5 cm) with a 1-year local PFS being the primary endpoint.

Approximately 80% of patients with CRLM are initially not suitable for curative resection due to

tumor location, multifocality, bilobar disease manifestation, or insufficient liver function. A total of about 65% develop intrahepatic recurrence within three years, even with adjuvant systemic chemotherapy.[48] In turn, image-guided ablation techniques may be suitable alternatives and particularly favorable options for elderly, vulnerable CRLM patients with high risks for surgery.[49] Major indications for thermal ablation include rather small (<3 cm), solitary unresectable hepatic metastases in patients with comorbidities, or poor performance status. A recent randomized prospective clinical trial revealed that local ablation can improve OS in unresectable CRLM. In particular, RFA (± surgical resection) and chemotherapy *versus* chemotherapy alone demonstrated a significantly prolonged 8-year OS of 35.9% *versus* 8.9%, respectively.[5] These results may also partially be transferable to brachytherapy.

With regards to brachytherapy, a prior retrospective analysis including 80 patients with 179 unresectable CRLM (mean diameter: 29 mm, range 8–107 mm) reported local recurrence in 23 (12.9 %) patients and systemic tumor progression in 50 patients (62.5 %), within a mean follow-up time of 16.9 months. The median OS was 18 months and TTP was 6 months.[28]

In our study, the mean target tumor diameter of the CRLM was 40.00 ± 24.07mm, while the median time until local recurrence was 12.43 (0.73–21.90) months, which was significantly shorter than in HCC [36.83 (1.33–40.27); $p = 0.001$]. Unlike HCC, pathology reports demonstrate that CRLMs have a more active peripheral tumor cell growth and abundant blood supply, whereas both primary and metachronous HCC foci are characterized by predominantly arterial neovascularization.[19] These features may also be assessable on MRI as subcapsular distribution and peritumoral enhancement, which are common findings in CRLM.[50]

To address the limitations of brachytherapy alone in CRLM, a recent prospective study including 23 patients with 47 unresectable CRLMs (mean diameter: 62 ± 19 mm) proved the feasibility and safety of combined irinotecan chemoembolization and CT-guided brachytherapy with a median OS, PFS, and TTP of 8, 4, and 6 months, respectively.[51] However, randomized controlled trials to determine superiority of any of the approaches are warranted.

During the follow-up of the study, patients did not receive any specific or standardized treatment. Given that cancer patients usually receive a multidisciplinary treatment regimen, with several therapeutic approaches depending on their stage of disease, we did not censor patients with additional therapies that were not specifically directed to the previous target lesions (e.g., systemic therapies). It should be noted, however, that systemic (chemo)therapies were paused at least two weeks prior to brachytherapy and resumed two weeks after brachytherapy at the earliest.

Our study has several limitations. Due to the rerospective design, some clinical data could not be reported for all patients (i.e., performance score). In addition, a pathological diagnosis was not available for all HCCs and CRLMs but common MRI diagnostic criteria were used that allow for highly specific non-invasive diagnosis of HCCs and CRLMs, as recommended by practice guidelines.[31,50] Tumor response was assessed by RECIST 1.1, which may not be entirely representative of the response of the tumor to brachytherapy that is indicated by gradual signal alterations rather than tumor shrinkage on MRI. However, RECIST 1.1 was applied, as it is the most widely-used criteria for solid tumors. It can also reliably detect tumor progression in terms of new lesions as well as an increase in size of the target lesion >20%, which is not typically expected after brachytherapy. Lastly, no median OS was reached in HCC, as many patients could not be traced to the endpoint of OS. However, PFS was the primary study endpoint; most patients presented with progression prior to death in both HCC and CRLM.

In conclusion, brachytherapy proved to achieve better tumor control of HCC than CRLM in terms of overall PFS and local tumor recurrence. With growing treatment possibilities for both HCC and CRLM, identifying the most beneficial therapeutic regimen for individual patients and disease stages becomes increasingly challenging. Our findings may help to design disease-specific surveillance strategies that highlight the efficacy and strengths of brachytherapy in primary and secondary liver cancer and elucidate the potential benefits of combination approaches with adjuvant loco-regional or immuno-oncological therapies.

Acknowledgements

H.X. and Y.H. are fellows of the Chinese Scholarship Council. L.J.S. is a fellow of the BIH

Charité Junior Clinician Scientist Program funded by the Charité – Universitätsmedizin Berlin and the Berlin Institute of Health.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author to editors and referees at submission, and to readers upon reasonable request.

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Curriculum Vitae

Personal Data

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection

Publication list

Xu H, Schmidt R, Hamm CA, Schober IT, He Y, Böning G, Jonczyk M, Hamm B, Gebauer B, Savic LJ. Comparison of intrahepatic progression patterns of hepatocellular carcinoma and colorectal liver metastases following CT-guided high dose-rate brachytherapy. Ther Adv Med Oncol. 2021, Vol. 13: 1–14DOI: 10.1177/17588359211042304

Acknowledgments

Upon the completion of this thesis, I am grateful to those who have offered me encouragement and support during the course of my study.

First and foremost, special acknowledgment is given to my respectable supervisor PD Dr. Lynn Jeanette Savic whose patient instructions and constructive suggestions have been beneficial to me a lot.

Second, particular thanks go to Prof. Dr. Bernd Hamm who invited me to the Department of Radiology at Charité and offered me the opportunity to work in our group. Also, thanks to Robin Schmidt, Isabel Schobert, Charlie Hamm and all the other MITT lab colleagues and professors who have taught me and gave me advice and instructions and generously supported me during the past years. Moreover, I would like to present my thanks to the China Scholarship Council who have supported me during my research period.

Last but not least, I am deeply indebted to my family and friends, who have helped me and shared with me my worries, frustrations, and happiness.