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Cholangiocarcinoma: CT-guided High-Dose Rate Brachytherapy (CT-HDRBT) for Limited (<4 cm) and Large (>4 cm) Tumors

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Abstract. *Background/Aim: Thermal-ablative therapies are limited to tumors of 3-4 cm diameter. The purpose of this study was to evaluate the local tumor control (LTC) of CT-guided High-Dose-Rate-Brachytherapy (CT-HDRBT) for ablation of cholangiocarcinomas (CCA) ≥4 cm compared to smaller tumors. Patients and Methods: Sixty-one patients (tumors: 142, interventions: 91) were treated from March 2008 to January 2017. LTC, progression-free survival (PFS) and overall survival (OS) after first CT-HDRBT were identified for two subgroups (A:<4 cm, B:≥4 cm) and the influence of coverage and target-dose were evaluated. Log-Rank- and Mann-Whitney-U-Tests were performed for statistical analyses with p-values <0.05 considered as significant. Results: Better coverage was achieved for smaller tumors (A: 99.22-0.25%, B: 95.10-1.40%, p<0.001). LTC was better in subgroup A (A: 8, B: 6 months, p=0.006). Larger tumors (4-7 cm) with incomplete coverage showed the poorest LTC (p=0.032). There were no statistical significances in PFS (A: 5, B: 3 months, p=0.597) and OS (A:15.5; B:10.0 months, p=0.107). Conclusion: CT-HDRBT is sufficient in CCA ≥4 cm, if full coverage with therapeutic doses can be achieved.*

Cholangiocarcinoma (CCA) is a rare tumor entity and surgery is the only potentially curative treatment option for these patients (1). However, even for curatively intended resection, 5-year survival rates of 20-35% with a median survival ranging from 12 to 36 months are as disappointing as 5-year survival rates of 5-10% with a median survival of 6 to 12 months for patients with unresectable CCA (2-11). Unfortunately, many patients present with advanced tumor stages because of fast tumor progression, so that they are not suitable for primary resection (12).

Although, intrahepatic (iCCA), perihilar (pCCA) and ductal CCA (dCCA) belong histologically to different tumor entities, there are subsumed for the available treatment options. Valle *et al*. have shown in a heterogeneous population of 410 patients with locally advanced or metastatic tumors that chemotherapy with gemcitabine alone was associated with a shorter median overall survival of 8.1 months compared to gemcitabine and cisplatin with 11.7 months (13).

Additional interventional local treatment options are gaining more importance, especially for patients who are not eligible for surgery. Radiofrequency ablation (RFA) is supposed to completely coagulate the tumor by eventually expanding the ablation area up to 5 cm in diameter (14, 15). However, Teng *et al*. have demonstrated in a hepatocellular carcinoma (HCC) population that ablation margins <5 mm were significantly associated with higher rates of local recurrence (16).

Microwave ablation (MWA) might be a further treatment option as this modality is less prone to heat sink effects enabling larger coagulation diameters. Yu *et al*. published a retrospective analysis of 24 MWA ablations in cholangiocarinomas and maximum diamteters of 3.2±1.9 cm with a local recurrence rate of 25% (17). Nevertheless, thermal ablation is limited to tumor sizes of approximately 3-4 cm (18).

In 2002, computed tomography-guided high-dose-rate-brachytherapy (CT-HDRBT) was established as a further local treatment option with promising results in different tumor entities and even for tumor diameters greater 7 cm in HCC patients (19-22). However, previous studies revealed

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that large tumor size and multiple tumors are independent risk factors in CCA (3).

The purpose of this study was to evaluate the efficacy of CT-HDRBT for ablation of CCA larger than 4 cm in diameter compared to smaller tumors. Primary study endpoint is the lesion-based local tumor control. Secondary endpoints are the patient-based progression-free survival and overall survival.

Patients and Methods

Patients. In this retrospective, single-center study, 61 consecutive patients with cholangiocarcinoma (CCA) (mean age: 66-12; m: 38, w: 23) were treated with CT-HDRBT between March 2008 and January 2017. A minority of patients was included in a previous study with different aims and shorter follow-up periods. Patients had either primary iCCA or intrahepatic metastasis of a previously resected iCCA, pCCA, or dCCA. All patients were referred by oncologists or surgeons for treatment. Indication was confirmed by an interdisciplinary tumor board. Institutional ethics committee approval and written informed consent were obtained.

Local brachytherapy was contraindicated in cases of elevated total bilirubin levels greater than 2.5 mg/dl. Patients with extended cholestasis were provided with internal biliary drainage before treatment. Further contraindications included disseminated liver tumor spread (N>5), impaired coagulation (platelets<50,000/μl, prothrombin time <50%, activated partial thromboplastin time >50s) and massive ascites. Biliodigestive anastomosis, *e.g.* after Whipple procedure, was not a contraindication for CT-HDRBT, but these patients received a prophylactic antibiosis 1 day before treatment and 10 days after the procedure with oral ciprofloxacin.

All patients received a liver specific, contrast enhanced magnetic resonance imaging (MRI) using gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (Gd-EOB-DTPA, Primovist, Bayer Pharma, Leverkusen, Germany) for assessment of technical feasibility and exact tumor extent one day before treatment (Figure 1).

Procedure. All therapies were performed under mild intravenous analgosedation using midazolam and fentanyl as well as local anesthesia with lidocaine. First, direct percutaneous punctures of the tumors were performed using a 17 G needle under CT-fluoroscopy. Second, a 6 F angiographic sheath (CORDIS, Cardinal Health, AVANTI+, 6F, 23 cm length, Miami Lakes, FL, USA) was inserted over a 0.035" guide wire (Amplatz Super Stiff, Boston Scientific, Natick, MA, USA) in Seldinger technique. Last, the 6 F afterloading catheter (Primed, Halberstadt, Germany) was placed through the 6 F sheath into the target tumor. Contrast-enhanced CT ensures proper catheter positioning and these images were used for radiation planning. Additionally, these images could exclude early complications such as hemorrhage or pneumothorax.

In the following, these CT images were used for 3D radiation planning (Brachyvision, Varian Medical Systems, Palo Alto, CA, USA) performed by a radiologist together with a radiation oncologist (Figure 1). The target volume for radiation treatment, the clinical target volume (CTV), included the usually hypovascular tumor and the hyperenhancing peritumoral rim. Catheters, CTV, and adjacent risk structures were registered and calculation of the brachytherapy plan was performed including dwell times and locations of the iridium-192 source (Gammamed, Varian Medical Systems, Palo Alto, CA, USA). The intended tumor-enclosing target dose was 20 Gy allowing a much higher dose in the tumor center around the brachytherapy catheters. However, the target dose could be reduced in favor of adjoining risk structures.

After completed therapy, catheters were drawn out and puncture routes were occluded using Gelita Tampon (B. Braun Surgical, S.A., Rubi, Spain) torpedos during sheath removal.

Follow-up. A continuous follow up was provided including clinical visits and liver MRI using Gd-EOB-DTPA at 8 weeks and afterwards every 3 months after therapy (Figure 1). Chest CT was performed within the oncologic staging every 6 months. In cases of local tumor progression or new hepatic tumor lesions an additional CT-HDRBT was offered, if feasible.

Definitions. Endpoints of this study were the median duration of local tumor control (LTC), progression-free survival (PFS) and overall survival (OS). Moreover, local tumor control rate (LTC rate), progression-free survival rates (PFS rate) and overall survival rates (OS rates) were calculated for 0.5-, 1-, 2-, 3- and 5-years. LTC was defined as a progress of any CT-HDRBT-treated tumor after its radioablation, including primary therapy failures and later tumor recurrences. PFS was calculated from the date of first tumor ablation to any intra- or extrahepatic tumor progress. OS was determined as interval from first CT-HDRBT to the date of death or last date of follow up.

Analysis and statistics. Each tumor size, CTV, target dose, number of catheters, tumor coverage as well as additional therapies were recorded. LTC of each tumor, PFS after primary therapy, and OS after first CT-HDRBT were assessed using the Kaplan-Meier method. Patients lost to follow up were censored. Statistical analysis included the Log Rank test and the Mann-Whitney *U*-test to compare two subgroups of patients with tumors smaller (group A) or equal and greater 4 cm (group B) using SPSS Statistics (Version 25, Armonk, New York, USA) with p-values <0.05 considered significant. Moreover, further subgroup analysis of group B was performed (B1: 4-7 cm ablated with any target dose >12 Gy and up to 99.0% coverage, B2: 4-7 cm ablated with at least 20 Gy and >99.0% coverage, B3: >7 cm). The largest treated tumor defined subgroup affiliation.

Results

All interventions were successfully completed. Sixty-one patients were treated in 94 interventions with a total of 142 tumors. Twenty-eight patients underwent resection prior first ablation and 33 patients were treated due to primary CCA. Thirty-five patients underwent a single treatment session. Seventeen patients received 2 CT-HDRBT sessions, whereas 24 ablations in 12 patients were scheduled for sequential 2-step therapy due to large tumor volumes, multiple liver tumors or adjacent risk structures (Figure 2), 6 patients underwent 3 treatments, 2 patients received 4 brachytherapies and 1 patient attained 5 treatments. Thirty-five out of 61 patients deceased during the follow up period.

Intrahepatic CCA was the most frequently treated tumor entity (Table I). In subgroup A, average tumor diameters of

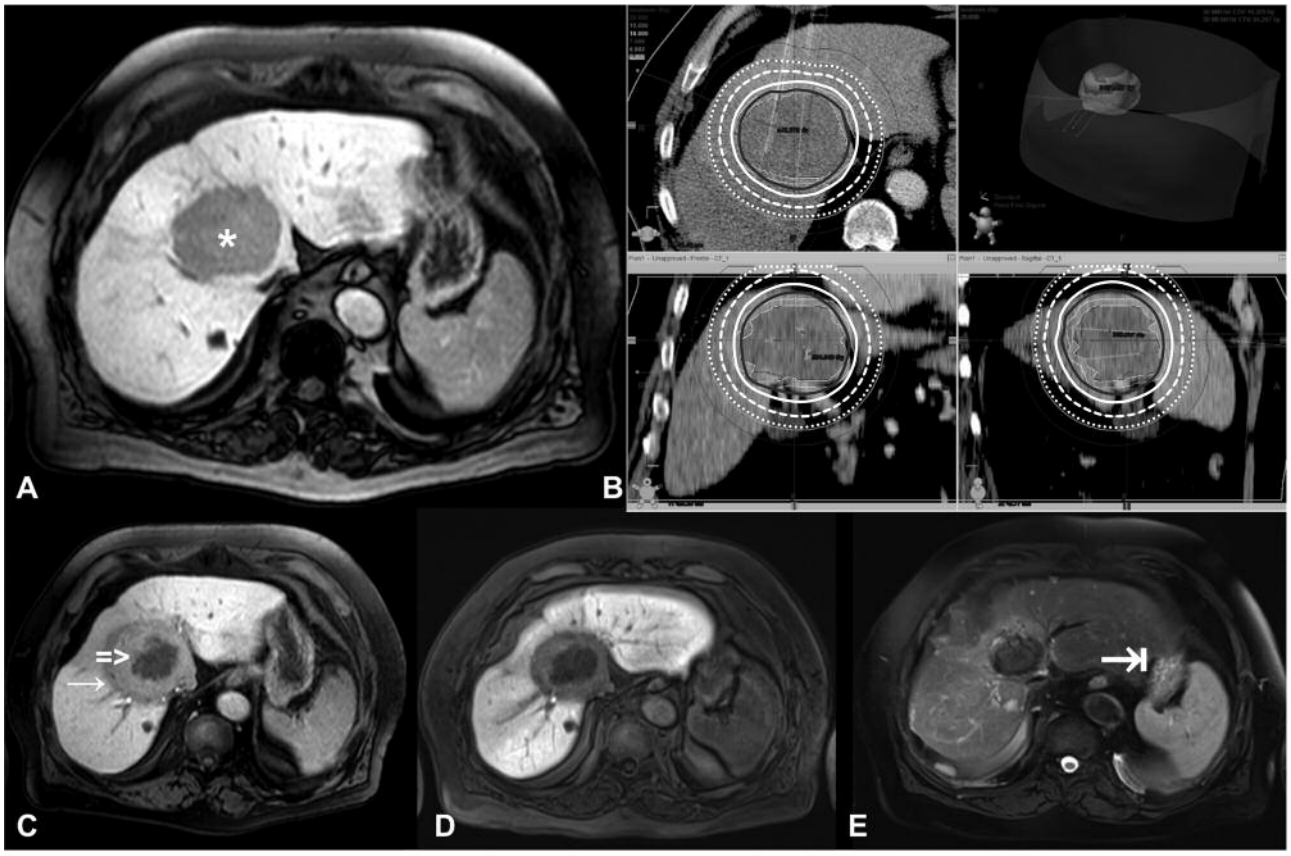

Figure 1. *A) Initial gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid MRI with primary cholangiocarcinoma (*), B) radiation plan, grey area = clinical target volume, gray solid line 20 Gy, white solid line 15 Gy, white dashed line 10 Gy, white dotted line 7 Gy, C) 1st follow-up after 8 weeks ≥ shrinking tumor volume, → ablation margin of surrounding liver tissue, D) 2nd follow-up after 5 months, E) 8th follow-up after 30 months with native MRI: T2 Turbo Spin Echo Fat Sat with good local tumor control, but new metastasis in segment 2 (→|).*

20.41±1.19 mm ranging from 10 mm to 38 mm and in subgroup B tumor diameters of 69.25±3.53 mm ranging from 40 mm to 148 mm, were treated.

Subgroup analysis revealed that a better coverage could be achieved for smaller tumors (A: 99.22±0.25 %, B: 95.10±1.40 %, $p<0.001$; Table II). Approximately 41% of the therapies in group B were performed in an intended 2 step sequential treatment, treating a partial tumor volume during first CT-HDRBT, followed by a second treatment after 6-8 weeks with treatment of the remaining tumor volume. The complete CTV could not be irradiated with 20 Gy in 44% in group B and a dose reduction was required, whereas 91% of the CTVs in group A received the full target dose of 20 Gy. In median, more tumors were treated per session in group A (A: 2, B: 1; $p<0.001$).

The LTC rates after 0.5-, 1-, 2-, 3- and 5-years were higher for patients with tumors measuring <4 cm (98%/87%/72%/72%/72%) than for larger tumors (89%/78%/37%/37%/37%) resulting in a statistically better median local tumor control in group A (A: 8 months, B: 6 months, $p=0.006$; Table III, Figure 3). Further analysis of group B (Figure 4) revealed that patients with tumors measuring 4-7 cm ablated with target doses >12 Gy and a

Table I. *Treated entities.*

Entity	Number of patients (<4 cm/≥4 cm)
iCCA	43 (11/32)
pCCA	9 (4/5)
dCCA	6 (3/3)
Gallbladder carcinoma	3 (0/3)

iCCA, Intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; dCCA, ductal cholangiocarcinoma.

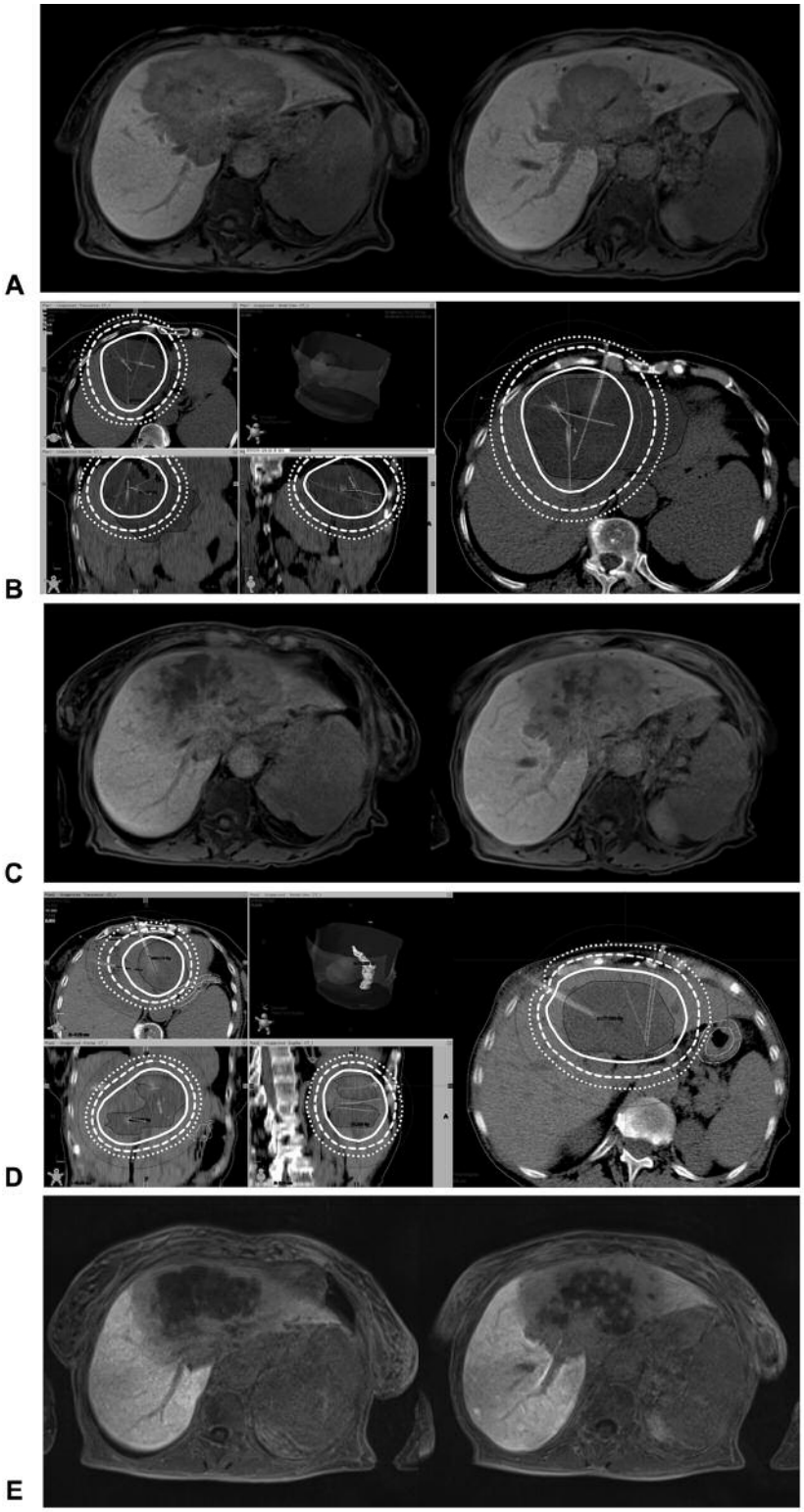

Figure 2. *Planning and follow-up magnet resonance imaging (MRI) in hepatobiliary phase (left: cranial liver segments, right: caudal liver segments) and radiation plan (grey area = clinical target volume, white solid line 15 Gy, white dashed line 10 Gy, white dotted line 7 Gy): A) 1st pre-treatment MRI, B) 1st computed-tomography-guided high-dose-rate-brachytherapy (CT-HDRBT) of the upper tumor compartment, C) 2nd pre-treatment MRI reveals already therapeutic response of the 1st session after 1.5 months, D) 2nd CT-HDRBT of the lower tumor compartment, E) follow-up MRI shows local tumor control of the sequentially treated tumor 3.5 months after first ablation.*

Table II. *Subgroup characteristics*.

	Group A <4 cm	Group ≥4 cm	Significance
Number of patients	18	43	
Sex (m/w)	12/6	26/17	
Number of interventions	35/94	59/94	
Number of treated tumors	75	67	
Pre-/post-interventional chemotherapy	6/4	13/8	
Pre-/post- interventional resection	16/2	12/0	
Diameter (mm)	20.41±1.19 (10-38)	69.25±3.53 (40-148)	
Clinical target volume (cm^3)	19.58±3.70 (1.4-86)	115.85±16.01 (2.3-566)	$p<0.001$
Target dose (20/15/12 Gy)	32/3/0	33/25/1	
Coverage with target dose (%)	99.22±0.25 (92.8-100)	95.10±1.40 (43.5-100)	$p<0.001$
Number of catheters (median)	2 (1-4)	3 (1-5)	p=0.001
Number of treated tumors/session (median)	2 (1-4)	1 (1-3)	$p<0.001$
Sequential treatment	0/35	24/59	$p=0.002$

Ranges are given in brackets (min–max).

Table III. *Survival data*.

	<4 cm	≥4 cm	Significance
LTC rates after 0.5-, 1-, 2-, 3- and 5-years (%)	98/87/72/72/72	89/78/37/37/37	
Median LTC (month)	8 (0-101)	6 (0-63)	$p=0.006$
PFS rates after 0.5-, 1-, 2-, 3- and 5-years (%)	41/35/24/24/16	39/25/17/17/17	
Median PFS (month)	5 (0-101)	3 (0-63)	$p=0.597$
OS rates after 0.5-, 1-, 2-, 3- and 5-years (%)	94/68/61/46/36	75/63/36/16/12	
Median OS (month)	15.5 (0-101)	10.0 (0-70)	$p=0.107$

LTC, Local tumor control; PFS, progression-free survival after first treatment; OS, overall survival after first treatment.

coverage up to 99.0% (B1) had the lowest LTC rate (83%/83%/14%/14%/n.a.; $p=0.032$) compared to patients with tumors measuring 4-7 cm ablated with a target dose of at least 20 Gy and a coverage >99.0% (B2: 93%/80%/60%/60%/60%) and patients with CCAs larger 7 cm (B3: 95%/83%/70%/70%/n.a.). However, the Log Rank test showed no significant differences between the subgroups A, B2 and B3 ($p=0.728$).

On the other hand, there was no statistical significance in the median PFS after first CT-HDRBT between both groups (A: 5 months, B: 3 months, $p=0.597$). Also, the median overall survival after first brachytherapy showed no statistical difference between both subgroups (A: 15.5 months; B: 10.0 months, $p=0.107$). The 5-year survival rate of the entire cohort was 15%. However, OS rates differed for tumors <4 cm (94%/68%/61%/46%/36%) and for tumors ≥4 cm (75%/63%/36%/16%/12%). Moreover, there was a tendency to a longer OS after first brachytherapy in afterloading technique for secondary compared to primary CCA ($p=0.062$; Figure 5).

Discussion

CT-HDRBT achieved sufficient LTC in patients with CCA independently from the tumor diameter even in larger tumors as long as a good coverage with a therapeutic dose could be applied. However, there were no statistical differences between both subgroups in progression-free and overall survival after first brachytherapy.

This study is limited to its monocentric and retrospective design as well as to a small number of patients. Furthermore, the study population was histologically heterogeneous and patients presented at different stages of their locally advanced or metastatic tumors with different pre- and post-interventional therapies such as chemotherapy or surgical resections (Table II). The integrity of brachytherapy was evaluated using follow up MRI imaging with liver specific contrast agents and was not histologically proven like in most studies concerning ablative therapies. Therefore, the tumor grading as an individual prognostic factor could not be provided in each case.

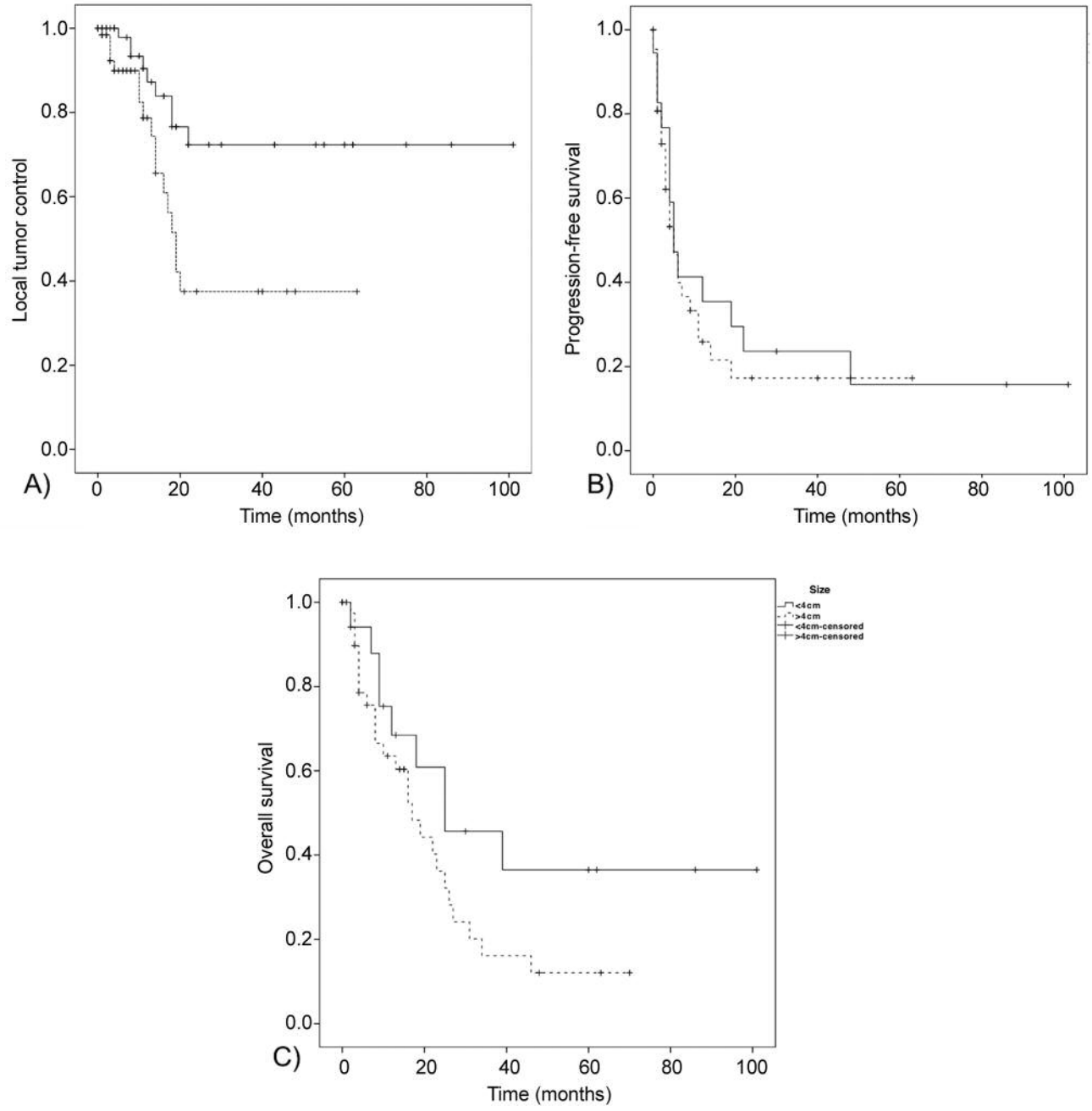

Figure 3. *Survival Analysis: A) Local tumor control, B) Progression-free survival after first treatment, C) Overall survival after first computed-tomography-guided high-dose-rate-brachytherapy. Solid line: Subgroup with cholangiocarcinoma <4 cm, dotted line: Subgroup ≥4 cm, +: censored cases.*

Surgery is the only potentially curative treatment option with 5-year survival rates of 20-35% and a median OS ranging from 12 to 36 months. Unresectable patients have shown 5-year survival rates of 5-10% with a median survival of 6 to 12 months (2-11). Nevertheless, patients being inappropriate for surgery because of tumor size, location, multifocal disease or restricted performance status require minimal invasive interventions. CT-HDRBT could increase the OS in the group of unresectable patients, if suitable for ablation therapy. In the present study, two patients became even eligible for additional resection after their first brachytherapy in the subgroup of tumors <4 cm. Earlier studies in a selective population have revealed that an intensive use of a combination of CT-HDRBT and surgical resection increased the median OS of patients

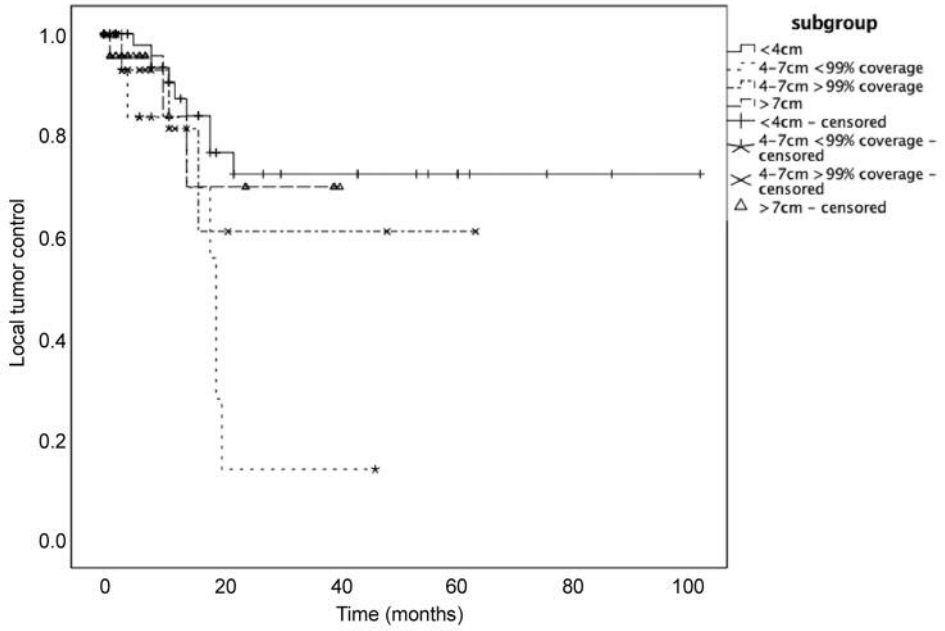

Figure 4. *Local tumor control – Subgroup analysis. Solid line: cholangiocarcinoma (CCA) <4 cm, dotted line: CCA 4-7 cm with target dose >12 Gy and coverage up to 99.0%, dashed and dotted line: CCA 4-7 cm with at least 20 Gy target dose and coverage >99.0%, dashed line: CCA >7 cm.*

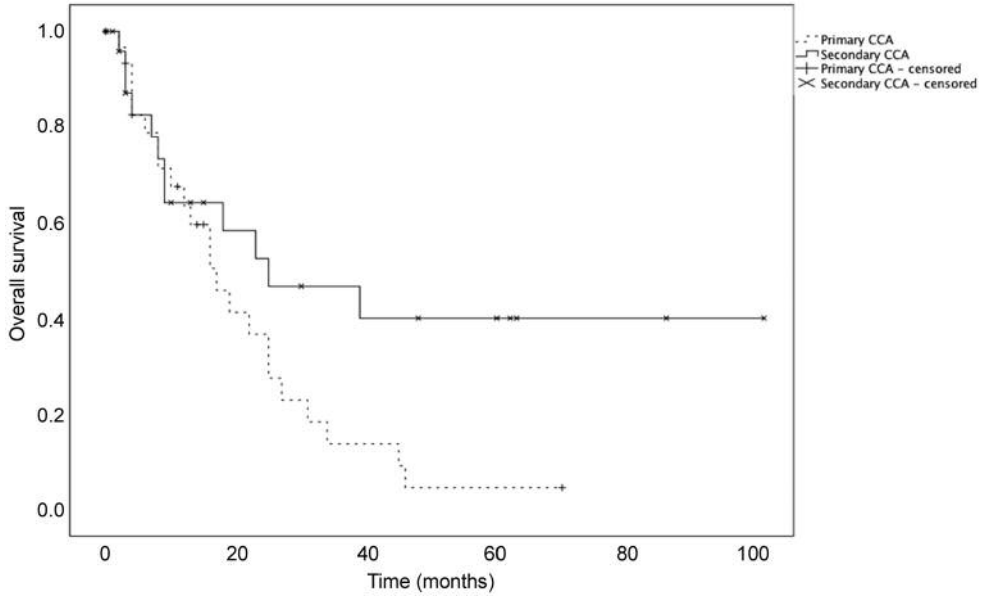

Figure 5. *Overall survival - Primary (dotted line) vs. secondary cholangiocarcinoma (solid line).*

after primary liver resection to 85 months with 1- and 5-year survival rates of 100% and 78.7%. One-year and 5-year survival rates after recurrence treatment were reported with 77.1% and 51.4% (20).

Chemotherapy is indicated in all advanced and metastatic CCA resulting in median overall survivals of 11.7 months for a dual chemotherapy with gemcitabine and cisplatin (23). CT-HDRBT might prolong intervals before and in between

chemotherapy as a local treatment option even in patients being not eligible for resection or thermal ablation. Herein, in patients receiving CT-HDRBT with tumors smaller 4 cm, median survival rates of 15.5 months were found. Only 4 patients received chemotherapy after their first session of brachytherapy. In the subgroup of larger tumors, a median OS of 10.0 months was observed. Eight of these patients received chemotherapy after and 13 patients before the initial brachytherapy.

RFA is a well-established local treatment option. Kim *et al*. have reported in a series of 13 patients with 17 primary tumors smaller than 5 cm, despite of two tumors with treatment failures measuring 7 cm and 8 cm, a median OS of 38.5 months and a 5-year survival rate of 15% (24). Another study has reported 20 patients with 29 recurrent CCAs undergoing RFA with mean tumor sizes of 1.9 cm ranging from 0.7 cm to 4.4 cm with a median OS of 27.4 months and a 4-year survival rate of 21% (25). A pooled analysis of 7 studies performed by Han *et al*. focusing on RFA for treatment of primary and recurrent CCA revealed 1-, 3- and 5-year survival rates of 82%, 47% and 24%, which were better than CT-HDRBT results in the first year for tumors <4 cm but diverged after 3 years (68%/46%36%) (26). These results might be influenced by patient selection and tumor diameters. Chiou *et al*. have reported for radiofrequency ablation that tumors larger than 5 cm were difficult to ablate completely (27). Unlike RFA, CT-HDRBT is not affected by heat sink effects which allows therapies next to larger vessels and greater tumors.

Yu *et al*. have presented survival data after MWA alone of 15 patients with 24 tumors treated in 38 interventions. The average tumor size was 3.2±1.9 cm ranging from 1.3 cm to 9.9 cm. The OS rates after 6, 12, 24 months were 78.8%, 60.0%, and 60.0% which were higher with our findings in the subpopulation with tumor sizes <4 cm (94%/46%/36%) after the first year (17). However, Zhang *et al*. have reported PFS rates after 6, 12, and 24 months of 67.4%, 41.5% and 8.7% in a larger collective with 107 patients with 171 intrahepatic cholangiocarcinomas ≤5 cm after MWA being initially higher than in our subgroup with tumors <4 cm (41%/35%/24%) diverging considerably after 2 years. The reported OS rates after 1, 3 and 5 years were 93.5%, 39.6% and 7.9%, which lay throughout lower than in the subgroup A in the presented study (94%/46%/36%) (28).

Transarterial chemoembolization (TACE) is a widely accepted local treatment option in advanced hepatic malignancies such as HCC and CCA (29). On the one hand, conventional TACE (cTACE) procedures are performed with ethiodized oil (lipiodol) as embolic agent combined with chemotherapeutic agents such as gemicitabine, cisplatin, oxaliplatin, mitomycin-c, 5-FU, epirubicin, hydrocamptothecin, carboplatin or doxorubicin (30). Median OS for cTACE procedures in CCA patients has been found to range from 9.1 to 19.5 months (30). The longest OS of 19.5 months has been reported for a combined therapy with MWA by Yang *et al*. in cTACE patients with average tumor diameters of 3.6±1.1 cm (range 2.5-6.5 cm) (31). On the other hand, drug eluting bead TACE (DEB-TACE) was invented to increase intratumoral concentrations of the chemotherapeutic agent and to reduce systemic effects due to a controlled release of the anticancer agent from the microspheres (32). Again, different chemotherapeutic agents have been used, such as oxaliplatin, doxorubicin or irinotecan, resulting in median OS of 11.7 up to 30 months in patients with unresectable CCA (30).

Since first results suggested a beneficial influence of TACE to local ablative therapies, further studies exploring the efficiency of the combination of TACE with brachytherapy are clearly warranted to increase local tumor control for patients with tumors larger than 4 cm with coverage up to 99.0% and target doses >12 Gy by increasing the sensitivity of tumor to radiotherapy.

In this study, larger tumors were treated sequentially in a 6-week interval in 41% of cases in subgroup B to avoid radiation of risk structures like the stomach and to reduce the radiation dose in patients with large tumor volumes compared to their healthy liver tissue. Moreover, target doses were frequently reduced in larger tumors from 20 Gy to 15 Gy to ensure risk structure protection (Table II). Coverage of the entire tumor (>99.0%) with 20 Gy increased tumor response especially in CCA measuring 4-7 cm (Figure 4).

Radioembolization using ^{90}Y-microspheres could be another treatment option especially in cases of large and diffuse tumor volumes less than 50% of the total liver volume. Al Adra *et al*. have shown in a pooled analysis of 12 studies including 298 patients with a median OS of 15.5 months and response rate of 28% (33). However, percentage of liver involvement was heterogeneous in this analysis and only given in 6 out of 12 studies. Target tumor doses of 120 Gy inside the tumors were reported (34).

In conclusion, CT-HDRBT proved to achieve good LTC even in larger CCA with diameters ≥4 cm as long as a good coverage with therapeutic doses can be ensured. However, there was no significant difference in PFS or OS between the subgroups, thus, CT-HDRBT is a sufficient treatment option even in large CCA with diameters ≥4 cm.

Conflicts of Interest

BH receives grants from Siemens and Bayer Schering Pharma in relation to this study. All other authors declare that there is no actual or potential conflict of interest in relation to this article.

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