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Original Article

Stereotactic body radiotherapy dose and its impact on local control and overall survival of patients for locally advanced intrahepatic and extrahepatic cholangiocarcinoma

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ABSTRACT

Purpose: Non-resectable cholangiocarcinoma (CCC) is a significant therapeutic challenge because of bad prognosis. This study analyzed the outcome after SBRT for intra- and extrahepatic CCC.

Material and methods: Sixty-four patients with 82 CCC lesions from a retrospective multicenter database were analyzed. Available parameters were analyzed for local control (LC), overall survival (OS) and toxicity.

Results: Median follow-up time for patients alive was 35 months (range 7–91 months). Median overall survival (OS) time was 15 months; 2-year and 3-year OS rates were 32% and 21%. Median prescribed biological effective radiation dose (BED, $\alpha/\beta = 10$) was 67.2 Gy_{10} (range, 36–115 Gy_{10}; SD: 20 Gy_{10}) in median 8 fractions (range, 3–17; 95% CI: 3–12), median BED_{max} was 91 Gy_{10}. BED was the only prognostic factor for LC and OS. Patients receiving BED_{max} >91 Gy_{10} had a median OS of 24 months vs. 13 months for those receiving lower doses ($p = 0.008$). LC rates at 12 and 24 months were 91% and 80% for BED_{max} >91 Gy_{10} vs. 66% and 39% for lower doses ($p = 0.009$). Of note, tumor size and PTV were neither predictive nor prognostic for LC and OS. Treatment tolerance was good with 17% of grade 1 gastroduodenitis, 11% of grade 2–3 cholangitis and 4.7% of grade 3 gastrointestinal bleeding.

Conclusion: This is the largest reported series on SBRT in cholangiocarcinoma. Overall survival and local control were significantly improved after higher doses (BED) and tolerance was excellent.

Cholangiocarcinoma (CCC) is a cancer of the epithelial cells of bile ducts that can occur anywhere along the biliary tree between the ducts in the liver and the papilla of Vater which itself is excluded as a separate entity. Accordingly, the classification comprises intrahepatic cholangiocarcinoma (IHCCC), perihilar cholangiocarcinoma (PHCCC) and extrahepatic cholangiocarcinoma (EHCCC). IHCCC only accounts for about 10% of the cholangiocarcinomas with a rising incidence in Europe whereas PHCCC is responsible for up to two thirds of all tumors and about one quarter of the tumors are EHCCC [3]. Surgery is the mainstay of therapy for EHCCC and deemed the only curative treatment resulting in median overall survival times of 28 months (range 9–53 months) [14,22]. However, for PHCCC resection rates are only 50% and for IHCCC 60% [16]. For patients with inoperable tumors survival rates dramatically drop to 7–12 months and standard therapy is chemotherapy with gemcitabine and cisplatin based on the results of the ABC-02 trial [20,25]. In addition, there is also a variety of local tumor-directed therapies for patients with intrahepatic lesions such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), selective internal radiotherapy (SIRT), and

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percutaneous radiotherapy which is not restricted to the liver but also technically feasible for PHCCC and EHCCC [3].

Up until recently, the role of percutaneous radiotherapy was very limited as with conventional methods it was not safe to treat volumes in the liver to doses that would result in durable local tumor control rates without the risk of severe liver damage [17]. This situation changed only after the introduction of technical advances including image guided radiotherapy (IGRT), high precision treatment setup and high precision beam delivery. Methods that use a small number of fractions of a high dose with high precision are termed stereotactic body radiotherapy (SBRT). SBRT is well suited to treat targets in but also around the liver as it not only delivers a high focal dose to achieve local tumor control but also adequately spares the non-tumor liver tissue [21].

A number of groups reported the use of SBRT for CCC. However, most of these studies were small in numbers with predominance on IHCCC with local control rates at two years between 65%-100% (reviewed in [15]). Additionally, a group from Texas recently used conventionally fractionated radiotherapy (15–30 fractions) to high biologically equivalent doses (BED) and demonstrated significantly improved local control with doses above the median BED of 80.5 Gy compared to lower doses for IHCCC lesions [22].

This current multicenter analysis was performed to identify the patterns of care in German speaking countries for CCC treated with SBRT. To our best knowledge this is the largest reported study on SBRT for this specific tumor entity. Intriguingly, the study not only comprised IHCCC but also a large number of PHCCC lesions and some inoperable EHCCC, and we were able to demonstrate that dose of radiotherapy was the only parameter that was predictive for local control and prognostic for overall survival.

Materials and methods

The analysis was based on a multicenter patterns-of-care SBRT database on primary liver cancer that was initiated by the working group 'Stereotactic Radiotherapy' of the German Society for Radiation Oncology (DEGRO). Dose and fractionation schedules varied by proximity of the lesion to organs at risk (OAR), by planning target volume (PTV) and by institution. The multicenter data collection and analysis were approved by the Ethics committee of the Kanton Zurich, Switzerland (BASEC-Nr. 2016-00744) and the data collections of the respective centers were approved by local ethics committees accordingly.

The motion management was categorized into simple (free breathing, abdominal compression) and advanced (breath-hold, gating, tracking) techniques. Image guided radiotherapy (IGRT) techniques were recorded (conebeam CT and stereoscopic kilovolt imaging). For 17 lesions where dose constraints for the OARs could not be achieved due to small overlaps with the PTV, a simultaneous integrated protection (SIP) dose prescription [20] was employed instead of reducing the dose to the entire PTV. Biological equivalent dose (BED) was defined as: $BED = D[1 + (d/\alpha/\beta)]$, where D is total dose (Gy), d is dose per fraction (Gy) and α/β (Gy) is a ratio from the linear-quadratic model describing the dose effect. We assumed an α/β ratio of 10 for tumor cells. Dose constraints were as published previously for 3–5 fractions and as shown in Suppl. Table 3 for $\geq$5 fractions [23].

The toxicity was scored using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.03 (CTCAE 2010). All toxicities that were observed within 90 days after treatment were considered to be acute and all other toxicities reported after >90 days were considered to be late toxicities.

Primary end points for this analysis were overall survival (OS) and local control (LC) in the PTV and its immediate proximity. Local control was defined as the absence of progression as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and calculated from the day of the first fraction of SBRT [7]. Secondary end points were toxicity and systemic disease progression. Lesions that progressed outside the immediate proximity of the PTV either in the liver or in lymph nodes were classified as regional progression and those developed in other organs as distant progression. Overall survival was calculated both, from the first day of SBRT and from diagnosis, until death. Follow-up was calculated from the first day of SBRT until the last date of follow-up.

Statistical analysis was performed with the software SPSS V24 (IBM, Armonk, NY). Survival was calculated from the first day of SBRT to last follow-up or death and separately from diagnosis to last follow-up or death. Survival and local control were calculated with the Kaplan–Meier method and uni- and multivariate analyses with the Cox proportional hazards model. Statistical significance was defined as a two-sided p-value < 0.05.

Results

Patient and tumor characteristics

Patient and treatment characteristics are summarized in Table 1. Within this database a total of 82 lesions in 64 patients with cholangiocarcinoma were treated with SBRT at nine German and Swiss centers between July 1999 and September 2016. The dose was most frequently prescribed to the 66% isodose (median) and at average to the 75% isodose with an inhomogeneous dose profile as typical for SBRT treatments. The most frequently used number of fractions was 3, 5, 10, and 12 fractions which were utilised in 28%, 12%, 13%, and 28%. Lesions treated with three fractions most commonly received 3 × 13–15 Gy (18%) and lesions treated with 12 fractions received 12 × 4 Gy (24%) prescribed to the isodose encompassing the PTV. Other technical details are summarized in Supplementary Table 1. The comparison of the size of the PTVs in the two groups with the most frequent number of fractions, 3 versus 12 fractions, was statistically significant ($p = 0.006$) with median volumes of 33 mL (range 5–772; SD 172) versus 244 mL (range 29–1876; SD 497). Baseline Karnofsky performance status was most frequently 80%, 90% or 100% (in 22%, 41% and 26% of the cases). However, prescribed BED correlated not statistically with PTV size (Table 2).

The median BED ratio of the maximal dose in the PTV divided by the prescribed dose was 1.4 (95% CI 1.03–2.29; range 1.0–2.40).

Median overall survival time of all 64 patients was 15 months (95% CI – months) from start of SBRT. The actuarial survival rate was 61% (57–65%) and 34% (32–37%) at one, and two years, respectively from the first day of radiotherapy (Fig. 1A). Median overall survival from diagnosis was 27 months (95% CI 24.9–28.5 months). The actuarial survival rate was 81% (77–85%) and 55% (51–59%) and 40% (37–43%) at one, two, and three years, respectively from diagnosis. In a total of 82 cholangiocarcinoma lesions treated with SBRT, 14 local relapses were observed and up to 37 months after SBRT corresponding to a total rate of 18%. The local control rates of 82 lesions after one, two, and three years were 89% (% CI 86–92%), 73% (68–77%), and 73% (67–79%), respectively (Fig. 1B) (Table 3).

Risk factors

Patient related factors such as age and gender did not impact on LC or OS. There was no difference in LC for intrahepatic compared to perihilar tumors (Suppl. Fig. 1). Also, the twelve patients who had more than a single treated lesion had no difference in survival and no inferior local control compared to patients with a single lesion. Similarly, non-SBRT treatment factors (prior or subsequent chemotherapy, prior surgery or non-surgical local therapy) did not impact on either of the two endpoints, LC or OS.

Table 1
Patient and treatment characteristics for our sample of 64 patients with 82 SBRT treatments.

Parameter	Number all tumors (Percent)	Median (Range)	Number of lesions (Percent)	Median (Range)	Number of lesions (Percent)	Median (Range)	Level of significance
	All lesions/patients		$BED_{10} \leq 67.2$ Gy		BED_{10} >67.2 Gy		
Age [years]	64 pts	64 (36–90)	42 pts	68 (36–90)	22 pts	69 (36–84)	0.853
Male gender	34 pts (53)		25 pts (60)		9 pts (41)		0.144
Number of lesions per patient	one: 52 (81) two: 9 (14) three: 1 (2) four: 2 (3	–	one: 34 (81) two: 6 (14) three: 1 (2) four: 1 (2)	–	one: 18 (82) two: 3 (14) three: 0 four: 1 (5)	–	n.s.
Location: - iCCC - pCCC - eCCC - n.a.	41 (50%) 31 (38%) 3 (4%) 7 (9%)	–	Total 50 23 (46%) 22 (44%) 1 (2%) 4 (8%)	–	Total 32 18 (56%) 9 (28%) 2 (6%) 3 (9%)	–	0.227 (intrahe-patic vs perihilar)
Diameter [cm]		4.4 (1–18)	52	5.1 (1.5–18)	30	4 (1–12)	0.025
PTV volume [mL]		114 (5–1876)		148 (6–1876)		67 (5–801)	0.041
Liver volume [mL]		1548 (843–3355)		1599 (843–3355)		1427 (1123–2284)	
Pre-treatment prior SBRT*[1] - none - surgery - local non-surgical - chemo	53 (64%) 13 (16%) 4 (5%) 20 (24%)	n.a.	37 (71) 6 (12) 1 (2) 10 (19)	n.a.	16 (53) 7 (23) 2 (7) 8 (27)	n.a.	
Histology yes	52/82	n.a.	33/52	n.a.	19/30	n.a.	
Cx after RT missing	27/82 11/82	n.a.	17/52 7	n.a.	10/30 4	n.a.	
BED of TDmax	–	96 (36–229)	–	79 (36–144)	–	152.5 (75–229)	
BED of Dmean GTV	–	80 (31–177)	–	69 (31–140)	–	133 (72–177)	

Abbreviations: BED = biological equivalent dose; Cx = chemotherapy; eCCC = extrahepatic cholangiocarcinoma; Gy = Gray; GTV = gross tumor volume; iCCC = intrahepatic cholangiocarcinoma; LC = local control; M = distant metastasis (TNM); n.a. = not available; n.s. = not significant, $p \geq 0.05$; pCC = perihilar cholangiocarcinoma; SBRT = stereotactic body radiotherapy; PTV = planning target volume; pts = patients; TDmax = maximum of the total dose; vs = versus.
[1] Multiple combinations are possible.

Table 2
Univariate analysis for local control and overall survival[§,]

Parameter	Local control		Overall survival	
	HR (95% CI)[‖]	$p^{§}$	HR (95% CI)[‖]	$p^{§}$
Age	–	0.068	–	0.950
Gender	–	0.391	–	0.937
KPS (80)	–	0.834	–	0.927
BED_{10} $D_{prescribed}$ (median 67.2 Gy)	**0.17 (0.04–0.74)**	**0.008**	–	0.439
BED_{10} D_{mean_GTV} (median 76 Gy)	**0.14 (0.04–0.52)**	**0.001**	–	0.074
BED_{10} D_{max} (median 91 Gy)	**0.25 (0.08–0.76)**	**0.009**	**0.47 (0.25–0.87)**	**0.008**
Prior chemo	–	0.195	–	0.834
Prior surgery	–	0.255	–	0.887
Prior local noninvasive	–	0.983	–	0.573
Additive chemo	–	0.952	–	0.117

[‖] = Logrank test, [§]Cox regression, [§]multivariate analysis did not show significant values.

However, local control was significantly higher for lesions treated with doses above the respective medians of the BED of the prescribed dose (67.2 Gy), of the mean BED to the PTV (75.0 Gy) and of the maximal BED in the PTV (91.0 Gy), $p = 0.008$, 0.001, 0.009, respectively (Fig. 2A). This did transfer into significantly prolonged overall survival for patients who were treated with maximal BED to the PTV above 91 Gy ($p = 0.008$; Fig. 2B). The ratio of the maximal BED divided by the prescribed BED was not statistically significant for local control but for overall survival ($p = 0.026$). None of the other tested parameters (e.g. age, gender, performance status, chemotherapy before or after SBRT, prior surgery, prior ablative therapy) had statistical impact neither on local control nor on overall survival. Multivariate analysis using Cox regression did not show statistical significance.

Toxicity

In general, SBRT was well tolerated. There were 11 episodes of grade 1 gastroduodenitis (17%). A further 11 episodes (17%) of grade ≥ 2 toxicities were observed and 7 of these were cholangitis which were treated by stent replacements, and in three patients grade 3 gastrointestinal (GI) bleedings were observed (4.7%) after follow-up times of 3.7, 4.3, and 12.6 months after SBRT in 12, 12, and 10 fractions respectively. The first patient had peritoneal progressive disease (PD) and pulmonary embolism treated with anticoagulation. Dose constraints to the stomach were respected (D_{max} was 49.4 $EQD2_3$ Gy, the $D_{0,5cc}$ was 25,7 $EQD2_3$ Gy and D_{5cc} was 20,0 $EQD2_3$ Gy). Gastric bleeding resumed after transfusion but the patient died from PD shortly thereafter. The second patient also had gastric bleeding which was successfully treated by argon

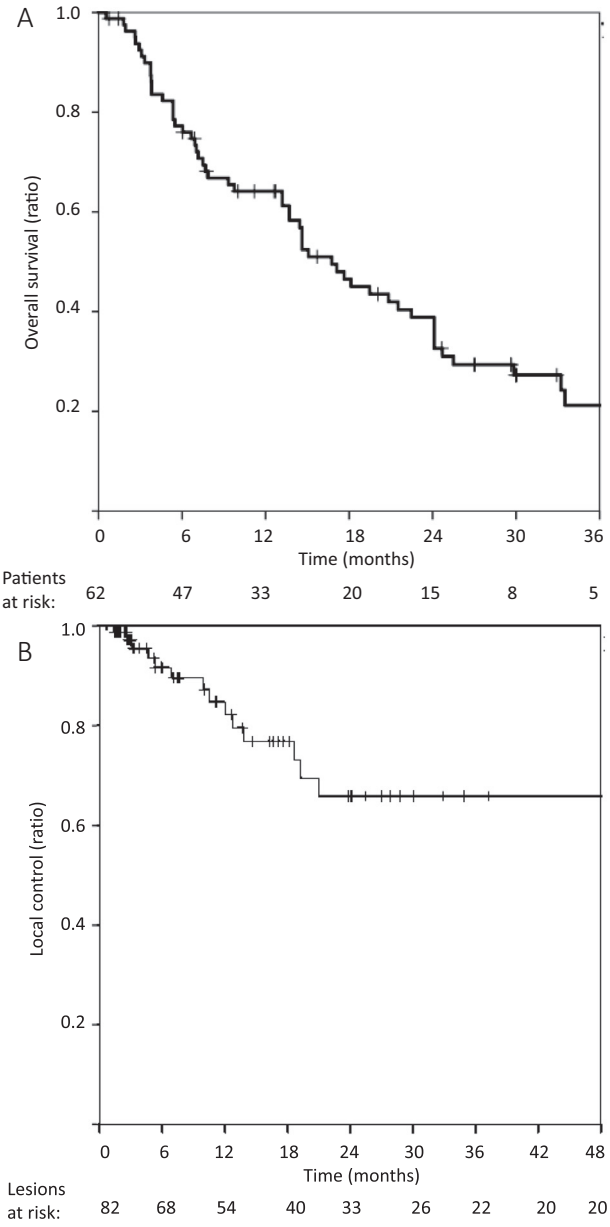

Fig. 1. Kaplan–Meier estimate of (A) OS in 64 patients with 82 lesions from the first day of radiotherapy with a median OS of 16.8 months. (B) Effect of radiation dose on local control (LC) and overall survival (OS) from the time of stereotactic body radiotherapy. Kaplan–Meier estimate of LC in 82 lesions.

plasma coagulation, and he had received (D_{max} was 62.0 $EQD2_3$ Gy, $D_{0.5cc}$ was 57.3 $EQD2_3$ Gy and D_{5cc} was 50.6 $EQD2_3$ Gy). The third patient developed a grade 3 duodenal ulcer bleeding more than a year after SBRT which was attributed to mechanical trauma from repetitive changes of bile duct stents (The D_{max} at the duodenum was 27,5 $EQD2_3$ Gy). No grade $\geq$ 4 toxicities were observed.

Discussion

To our best knowledge this is the largest series of SBRT for cholangiocarcinoma reported to date [9,13]. This study finds that escalating SBRT doses for cholangiocarcinoma results in improved local control which ultimately transforms into prolonged survival independently from tumor volume. Excellent tolerance of treatment was achieved by selection of an appropriate number of SBRT fractions and doses according to proximity of the target volume to bowel structures with as few as three fractions if target volumes were away from organs at risk and typically twelve fractions when target volumes were very close to such structures [4]. This was noticed throughout all participating institutions. Furthermore, prospective quality of life data for SBRT of liver lesions including CCC have demonstrated the good tolerance of this rather novel treatment modality [10].

Our multicenter study confirms previously reported findings of dose escalated conventionally fractionated radiotherapy [22]. This retrospective study reported that patients with intrahepatic CCC receiving BED_{10} >80.5 Gy benefited from higher dose by longer local control and overall survival. More evidence on the role of radiation dose in CCC was already reported in previous studies with conventionally fractionated radiotherapy [2,6]. An early dose-escalation study included 18 patients with intrahepatic CCC who were treated with a median dose of 61.5 Gy [6]. When dividing treatment groups at a cutoff dose of 70 Gy, patients with higher doses survived 16.4 months compared to 11 months when doses were lower. In a prospective phase II trial, Ben-Josef and coworkers delivered a median dose of 60.75 Gy (range 40–90 Gy) in two daily fractions of 1.5 Gy concurrently with hepatic arterial floxuridine chemotherapy in 128 patients of which 46 had intrahepatic cholangiocarcinoma [2]. This trial found that dose of radiotherapy was the only significant prognostic factor for overall survival. When median doses were higher than 75 Gy, the median OS was 24 months versus 15 months at lower doses ($p < 0.01$).

However, in our study the total treatment time was shorter due to the lower number of fractions given. This appears to be more convenient for the patients and might better fit into additional systematic treatment schedules, if they are applied. When comparing different dose parameters, PTV prescription dose, median dose to the GTV, and maximum dose in the tumor were all significantly predictive for local control. As for overall survival, only the maximum dose, which was at a median of 126% of the prescription dose, had a statistically significant impact. The importance of maximum doses that are clearly beyond the conventionally mandated 107% for conventionally fractionated radiotherapy is underpinned by our findings. The significance of high-dose peaks in the central tumor volume on local control was previously reported for SBRT for early-stage lung cancer and lung metastases [11,18] and for liver metastases [1]. Here, for the first time, we describe that high maximum doses >91 Gy_{10} correlated not only with local control but also with overall survival in patients with cholangiocarcinoma treated with SBRT. In this context it is also interesting to note that the mean GTV dose had the highest level of significance for local control in our series ($p = 0.001$). Mean dose to the GTV is a parameter that is closer correlated to the maximum dose as compared with the prescription dose. Therefore, when evaluating and reporting SBRT treatment series and dose volume histograms, especially in a multicenter setting, close attention should be paid to the high dose tails in the GTV and PTV as recommended by the recently published ICRU report 91 [19].

In comparison to our retrospective multicenter analysis, there are two prospective phase I studies on SBRT including patients with CCC, one from Princess Margret Hospital in Toronto and one from Stanford University [8,24,27]. Additionally there is a phase II trial. In the Toronto trial 10 of 41 patients had intrahepatic CCC with tumor volumes ranging from 10 to 465 cc, the remainder had hepatocellular carcinoma, and they were treated in six fractions with a dose escalation from 28 to 48 Gy (BED 33.6–86.4 Gy_{10}) [24]. All but two patients had $\leq$40 Gy total dose. The LC rate at 1 year was 65% and the median OS was 15 months. The group reported one patient each with biliary obstruction and bowel obstruction, respectively. Goodman and coworkers included five patients with intrahepatic CCC among a total of 26 patients with mostly hepatic metastases [8]. All patients had single fraction

Table 3
Local relapse by patient.

Patient	BED_{10} of prescribed dose (Gy)	BED_{10} of maximal dose (Gy)	PTV size (ml)	LC time (months)	Survival (months)	Fractions (number)	SIP	SIB	Lesions (number)	Diameter (cm)	PD M1	CA19-9 pre-SBRT (U/ml)	Age (years)
1	48.0	90.0	79.0	1.35	6.67	5	–	–	1	3	1	–	72.06
2	56.0	77.0	98.0	11.99	13.7	10	–	–	1	5	0	–	71.92
3	56.0	61.0	41.0	3.09	5.49	10	Yes	–	1	3	0	–	77.08
4	57.6	113.0	193.5	20.99	33.51	6	–	–	2	4.3	1	–	79.98
5	59.5	83.0	124	10.51	15.08	5	–	–	2	4	1	900	68.04
6	61.6	67.0	321	13.8	29.83	11	–	–	2	7	0	137	86.17
7	67.2	134.0	19.5	9.95	22.47	7	–	–	1	1.5	1	–	80.9
8	67.2	69.0	29	12.71	12.71	12	–	–	1	4	0	901	57.23
9	67.2	115.0	104.6	4.67	4.67	12	–	–	1	4.3	1	1075	85.06
10	67.2	75.0	106	6.87	19.48	12	–	–	1	3	0	183	87.43
11	67.2	125.0	264.8	19.25	24.64	7	–	–	4	5.7	1	–	78.87
12	67.2	86.0	1875.6	2.63	2.63	12	–	–	1	10	0	–	80.47
13	72.8	75.0	211	18.63	24.71	13	yes	–	1	7	0	3286	53.47
14[1]	102.3	115.0	37	5.29	6.05	12	yes	yes	1	5	0	28	51.77
Median	67.2	84.5	105.3	10.23	14.39	10.5	–	–	1	4.3	0	82.5	77.975

Abbreviations: BED = biological equivalent dose; Gy = Gray; LC = local control; M = distant metastasis (TNM); PD = progressive disease; PTV = planning target volume; SIB = simultaneous integrated boost; SBRT = stereotactic body radiotherapy; SIP = simultaneous integrated protection; U = unit.
[1] Postoperative bilioma, R1.

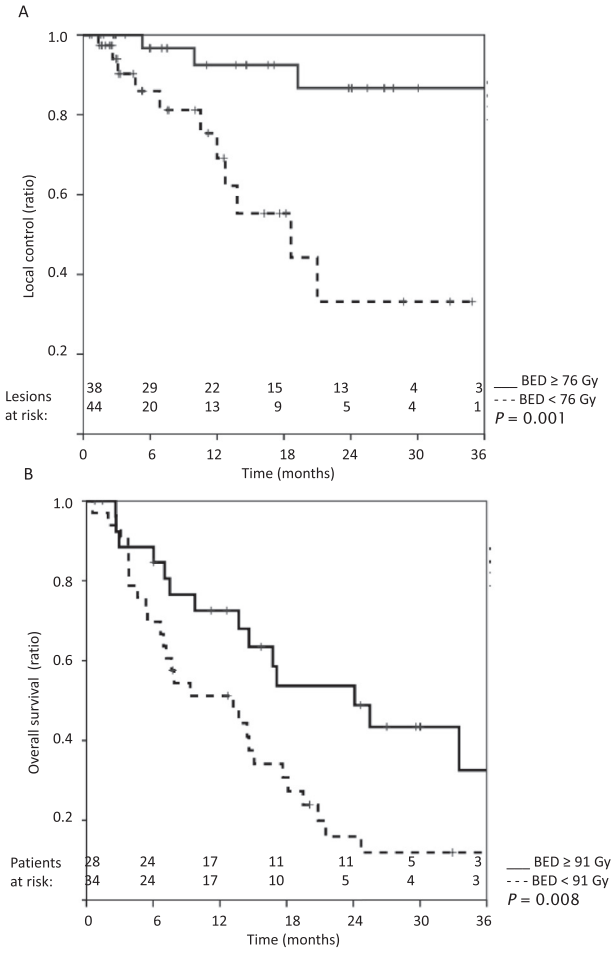

Fig. 2. (A) Effect of radiation dose on local control (LC) and (B) overall survival (OS) from the time of stereotactic body radiotherapy. Kaplan–Meier estimate of (A) LC in 82 lesions according to biologic equivalent dose (BED) of the D_{mean} less than 76 Gy or 76 Gy or more illustrate the superiority of the higher dose. (B) Kaplan–Meier estimate of OS in 64 patients with 82 lesions according to biologic equivalent dose (BED) of the D_{max} less than 91 Gy or 91 Gy or more illustrate the superiority of the higher dose.

SBRT of 18–30 Gy, but no specific LC and OS data were reported for patients with CCC. However, single fraction regimens of lesions close to bowel structures have been abandoned due to a significant increased risk of late gastrointestinal toxicities [5]. In the prospective Stanford trial two patients had late grade 2 gastrointestinal toxicities. Based on that, we would like to stress out that delivering SBRT dose schedules to lesions close to bowel structures, especially with high maximum doses, should be conducted carefully to avoid high grade toxicities. Employing higher fraction SBRT schedules beyond 1–5 fractions can be a strategy that has been adopted by a number of centers today [15].

Additionally to the prospective trials, there was a relatively large retrospective evaluation of SBRT for CCC published by a group from Korea. The series comprised of 58 lesions with half of the patients having unresectable and recurrent CCC. SBRT was delivered in 1 to 5 fractions at doses of 15–60 Gy [9]. Median OS at one year was 45% and LC rates at one and two years were 85% and 72%, respectively. In contrast to our results, the group reported 10% of grade ≥3 toxicities which were duodenal and gastric ulceration, perforation, cholangitis and bile duct stenosis. Higher rates of toxicities were also reported by the group of Kopek in 27 patients with almost exclusively intrahepatic CCC where 3 fractions to a total dose of 45 Gy were given [12]. High grade complications were observed in six patients with gastroduodenal ulcerations and in three with bile duct stenosis, whereas the LC rate was 85% at one year and median OS was 10.6 months (Kopek et al. 2010 [12]). Furthermore, a group from Boston reported on 34 patients with 42 mostly intrahepatic CCC treated with 3–5 fractions to a total dose between 24 and 45 Gy [13]. The LC rate at one year was 88% and median OS was 17 months. However, the group also described 4 patients with grade 3 toxicities which were ulceration, cholangitis and an intrahepatic abscess.

Limitations of the study include the retrospective multicenter nature of the analysis compromising completeness of data, especially on late toxicities, which need to be interpreted according to these circumstances. Also, the interval of recruitment ranged over many years which potentially could have led to a bias due to technical advances over time. Lack of histological confirmation in some patients with PHCCC is another limitation. Despite combined brush cytology and forceps biopsy histological confirmation of disease can be extremely difficult in PHCCC, and it was shown to

be positive in only 60% in an experienced center [26]. The diversity of fractionation and dosing regimens is however rather a strength than a weakness as this allowed the comparisons of high and low dose groups after calculation of BED values.

In conclusion, our analysis shows that biologically effective radiation dose for SBRT of cholangiocarcinoma impacts on both, local control and overall survival. The use of iso-effective treatment schedules by varying the number of treatment fractions may be a strategy to overcome toxicities that previously were reported after SBRT with a low number of fractions. In the future, prospective trials should further evaluate the use of SBRT for patients with cholangiocarcinoma.

Conflict of interest statement

None of the authors has a conflict of interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.11.015.

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