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ORIGINAL ARTICLE

Multicenter results of stereotactic body radiotherapy (SBRT) for non-resectable primary liver tumors

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Abstract

Background. An excess of 100 000 individuals are diagnosed with primary liver tumors every year in USA but less than 20% of those patients are amenable to definitive surgical management due to advanced local disease or comorbidities. Local therapies to arrest tumor growth have limited response and have shown no improvement on patient survival. Stereotactic body radiotherapy (SBRT) has emerged as an alternative local ablative therapy. The purpose of this study was to evaluate the tumor response to SBRT in a combined multicenter database. *Study design*. Patients with advanced hepatocellular carcinoma (HCC, n = 21) or intrahepatic cholangiocarcinoma (ICC, n = 11) treated with SBRT from four Academic Medical Centers were entered into a common database. Statistical analyses were performed for freedom from local progression (FFLP) and patient survival. *Results*. The overall FFLP for advanced HCC was 63% at a median follow-up of 12.9 months. Median tumor volume decreased from 334.2 to 135 cm^3 ($p < 0.004$). The median time to local progression was 6.3 months. The 1- and 2-years overall survival rates were 87% and 55%, respectively. Patients with ICC had an overall FFLP of 55.5% at a median follow-up of 7.8 months. The median time to local progression was 4.2 months and the six-month and one-year overall survival rates were 75% and 45%, respectively. The incidence of grade 1–2 toxicities, mostly nausea and fatigue, was 39.5%. Grade 3 and 4 toxicities were present in two and one patients, respectively. *Conclusion.* Higher rates of FFLP were achieved by SBRT in the treatment of primary liver malignancies with low toxicity.

More than 100 000 individuals are diagnosed with primary tumors of the liver every year in the USA [1] and untreated disease carries a poor prognosis [2]. Less than 20% of those tumors are amenable to definitive surgical management due to advanced local disease or other medical conditions that prohibit major surgery. Locoregional therapies (LRT) have been recommended in patients with hepatocellular carcinoma (HCC) as a form of palliation [3] or as a bridge for transplantation while in the waiting list [4]. LRT include radiofrequency ablation (RFA), cryoablation, microwave therapy, transarterial chemoembolization (TACE), Ytrium-90 embolization (Y-90) and percutaneous ethanol injection (PEI). The application of LRT are limited due to the size and number of tumors (< 3 cm for RFA), the liver function (TACE/Y-90 not recommended in patients with advanced liver disease), portal vein thrombosis and status of portal hypertension, distribution or vascular supply of the HCC [5–7].

Stereotactic radiosurgery (SRS) has shown to be very effective in the treatment of brain tumors with more than 60% response rates [8]. This modality allows for the delivery of large doses of radiation to

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a precise location while sparing the surrounding normal tissues. Building upon the experience with intracranial SRS, stereotactic body radiotherapy (SBRT) has been used to treat extracranial tumors in the chest, abdomen, and spine. Its use in the treatment of primary liver tumors is emerging; however we have encountered some physiologic and technical limitations. One of the challenges is the low tolerance of the liver to irradiation; this is very important when treating HCC, in which cirrhosis is frequently present. Therefore, it is very important to take into account the degree of underlying liver dysfunction. Radiation-induced liver disease (RILD) is a dose-limiting toxicity that can occur two weeks to four months after radiation therapy and this complication is mostly seen in patients with poor baseline liver function [9]. Another specific challenge faced when treating tumors in the chest and abdomen is that they are subject to respiratory motion, which is to be accounted for during computed tomography (CT) simulation, treatment planning, and treatment delivery in order to avoid irradiation of adjacent structures. There are four broad categories of respiratory control, namely, tumor motion dampening, respiratory gating, active breathing coordination [10] and tumor tracking. Tumor tracking can be accomplished by the use of an SBRT radiosurgery system, which consists of three key components: i) a special lightweight linear accelerator (LINAC); ii) a robotic arm which can point the LINAC from a wide variety of angles; and iii) a tumor tracking system. An average precision of 0.3 ± 0.1 mm can be achieved with the Cyberknife system [11].

The first reports of SBRT for liver tumors were done by Blomgren et al. in 1995 and 1998 [12,13], they treated 11 patients with primary liver tumors using 15–45 Gy in 1–3 fractions, obtaining 100% local control at one-year follow-up with minimal side effects. Based on these encouraging results, several centers around the world have work on phase I and phase II trials [14–17] aiming to describe the safety and efficacy profile of this treatment approach. The authors in this study have previously reported results in the treatment of primary and metastatic tumors of the liver [18–21]. The purpose of the present work was to determine tumor response to SBRT in patients with non-resectable and non-transplantable primary liver tumors in a pooled cohort of patients from four academic medical centers.

Material and methods

Patient population

IRB approved databases containing information from patients who underwent SBRT as treatment for primary liver tumors from four academic medical centers were merged into a common database for analysis. A total of 32 patients with 43 liver lesions treated from April 2001 to September 2010 were included. General inclusion criteria were: i) biopsy proven malignancy; ii) non-resectable, non-transplantable disease (Barcelona stage C and D); and iii) life expectancy of at least three months. Twenty-one patients were diagnosed with HCC and 11 patients with intrahepatic cholangiocarcinoma (ICC). All patients were initially assessed by a multidisciplinary team of hepatobiliary/transplant surgeons, radiation oncologists, medical oncologists, hepatologists and nurse practitioners to determine the stage of the tumor. In addition a Pub-med search (www.pubmed.gov) was performed using the key terms "stereotactic body radiotherapy", "stereotactic body radiosurgery", "hepatocellular carcinoma" and "cholangiocarcinoma" (June 8, 2011). All published articles using SBRT for HCC and ICC were reviewed, these were a total of 18 articles published from 1998 to 2011 with a total of 285 patients: HCC = 269 and ICC = 16 [13–17,22–34]. We did not include patients with primary/metastatic liver tumors from our previously published articles [18–21]. Articles were included in the final pooled review when the tumor response and clinical outcome data was clearly stratified by tumor type; patients who underwent liver transplantation after SBRT treatment were excluded. 12 studies with a total of 240 patients (HCC = 224 and ICC = 16) were included in the review [13,15,17,22,23,26–31,34].

SBRT technique

Although protocols differed from one Institution to another, the radiation plan for each patient at all centers was developed, reviewed and approved by a surgeon, a radiation oncologist, a medical oncologist and a physicist. All patients were staged with contrast enhanced CT, magnetic resonance imaging (MRI), and/or positron emission tomography scan (PET). Subsequent imaging was obtained for treatment plan development and contouring. Fiducial markers placement was achieved transcutaneously, by laparoscopic techniques or during open surgery with minimal complications [18–21]. Treatment planning and delivery technique varied by institution, mainly due to the type of equipment available.

Briefly, 18 patients were treated at University Hospitals-Case Medical Center/Cleveland Clinic. Their imaging was imported into the Multiplan™ treatment planning system version 2.05 (Accuray inc., Sunnyvale, CA, USA) and digitally fused in order to contour the gross tumor volume (GTV). An additional margin of about 3–5 mm was added in order to obtain the planning target volume (PTV).

Patients were immobilized for imaging using a custom Alpha Cradle (Smithers Medical Products, Akron, OH, USA) and fitted with a synchrony vest. One hundred to 300 6 MV X-ray beams were used for each plan. SBRT was delivered with the CyberKnife® system under real-time kilovoltage camera fiducial tracking and real-time respiratory motion modeling using a separate Synchrony® Respiratory Tracking System (Accuray inc.). This system is equipped with a robotic arm which can point the LINAC from up to 1600 non-coplanar targeting angles. For patients with HCC a median total dose of 30 Gy (range, 21–45 Gy), median equivalent dose in 2 Gy fractions (EQD2) = 50 Gy, and ICC patients got a median total dose of 37.5 Gy (range, 22.5–37.5 Gy), median EQD2 = 70.3 Gy. All treatments were given in 3 fractions at the 70% isodose line (range, 60–75%) [19].

Eight patients were treated at Memorial Sloan-Kettering Cancer Center. CT planning images were obtained in the treatment position using a custom Alpha Cradle. The GTV was delineated using the Eclipse™ treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). Liver lesions were outlined on the various respiratory phases on 4D-CT scans. An additional margin of about 3–5 mm was added to obtain the PTV. Planning images were transferred to the Multiplan™ treatment planning system (Accuray inc.). Patients were treated with the CyberKnife® system using the Synchrony® Respiratory Tracking System (Accuray Inc.). HCC patients received a median total dose of 22 Gy (range, 18–26 Gy), median EQD2 = 58.6 Gy and ICC patients received a median total dose of 30 Gy (range, 22–30 Gy), median EQD2 = 100. All doses were given in a single fraction using a 75% isodose line [18].

Six patients were treated at University of Rochester Medical Center. They were immobilized using the Novalis ExacTrac® patient positioning platform (BrainLAB AG, Heimstetten, Germany) which consist in a vacuum cushion bag for positioning and external body fiducial markers monitored by two ceiling mounted infrared cameras. Respiratory gating was obtained using a relaxed, end-expiratory breath-hold technique. Treatment planning was performed using the BrainScan® treatment planning system (BrainLAB). The GTV was contoured in CT scans fused with MRI and/or PET scans, when available. The PTV was generated with an expansion of the GTV of 10 mm in the craniocaudal direction and 7 mm in other directions. Treatment was prescribed to the 100% isodose line, with the 80% isodose line covering the PTV. SBRT was delivered with the Novalis™ linear accelerator system by using conformal arcs or multiple fixed coplanar beams. The dose per fraction and total dose were determined using the dose volume histogram of organs at risk. HCC patients received a median total dose of 47 Gy (range, 44–50 Gy), median EQD2 = 57.6 and the patient with ICC received 50 Gy, EQD2 = 62.5 Gy. Total doses were given in 10 Gy fractions over two weeks [20,21]

Assessment of treatment response

Follow-up of patients included a full physical exam, blood work and imaging studies (CT, MRI and/or PET scans). They were scheduled every three months for two years after SBRT. Patients who survived >2 years were assessed every three to six months depending upon clinical needs. The maximum tumor diameter and the GTV were measured exporting the images to the SBRT planning system (Multiplan™ or BrainScan®). Freedom from local progression (FFLP) was defined as an absence of progression of the targeted lesion. Tumor response to SBRT was graded using RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors version 1.1) [35,36]. This system has four tumor response grades: *Complete Response (CR)* or disappearance of all target lesions; *Partial Response (PR)* when at least a 30% decrease in the sum of the longest diameter (LD) of target lesions was observed, taking as reference the baseline sum of the LD; *Progressive disease (PD)* was granted when at least a 20% increase in the sum of the LD of target lesions was noted, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions; *Stable disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started [36]. In order to further evaluate partial tumor responses we used our previously published grading system based on tumor volume [19]. *Partial response grade I*: At least a 10% decrease in tumor volume but less than 30% from original tumor volume; *Partial response grade II*: A decrease in volume $\geq 30\%$ but $<50\%$ from original tumor volume; *Partial response grade III*: A decrease in tumor volume $\geq 50\%$. In the case of no change in tumor volume but vanishing of the enhancement or PET activity; this cases were scored as a grade III partial response.

Recurrences were also graded with our previously published scale [19]. *Grade 1*: local recurrence (tumor progression within or at the periphery of the radiation field) with two subgroups, *Grade 1a*: 1 local recurrence and *Grade 1b*: >1 local recurrences; *Grade 2*: Distant intra-abdominal recurrence (new tumor >3 cm away from the radiation field or in another organ); *Grade 3*: distant extra-abdominal recurrence; and *Grade 4*: A combination of local and distant recurrences.

Adverse events

Adverse events after SBRT were graded on 1–5 scale according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v3.0). Causes were attributed to either placement of fiducial markers, radiation therapy, chemotherapy or related to medical comorbidities.

Statistical analysis

A common database of clinical, imaging and SBRT variables for each patient was created with the collaboration of the four medical centers. Subject and tumor characteristics were expressed in median, mean, range and percentages. Paired t-tests were used to compare tumor volume before and after treatment. Kaplan-Meier product-limit curves were generated to calculate overall survival (OS) and FFLP. OS was calculated from the first date of SBRT to the day of last follow-up or death. Statistical routines were performed using JMP Statistical Discovery Software version 9.0 (SAS Institute, Cary, NC, USA). Two-sided p-values < 0.05 were considered statistically significant.

Results

The demographic variables of 32 patients treated by SBRT for non-resectable primary liver tumors and the characteristics of their malignant condition are summarized on Table I. Patients with HCC consisted of 16 men and 5 women, with a median age of 72 years. Their MELD score was 12 (median) and most of patients were Child-A. Seventy six point two percent of the patients had a single lesion, 23.8% had multicentric lesions and 9.5% of them presented with distant metastases. The median of their GTV was 334.2 cm^3 (range, 9.5–1913.8) treated with a total dose of 30 Gy in 3 fractions at an isodose line

Table I. Demographics and baseline tumor characteristics of patients with non-resectable primary liver tumors treated with SBRT.

	HCC		ICC	
	Current series	Literature†	Current series	Literature††
Number of patients	21	224	11	16
Age (years)				
Median (range)	72 (47–88)	(23–90)	66 (43–86)	(49–79)
Gender				
Male:Female	3.2:1	2.7:1	1.2:1	2:1
MELD score	12 (7–21)	–	–	–
Child-Pugh score	6 (5 – 8)	–	–	–
Institution (No of patients)				
UHCMC/CC	13	–	5	–
MSK	3	–	5	–
URMC	5	–	1	–
Prior therapy (%)				
Resection	9.5	8.7	50	9.1
RFA	4.8	11.3	27.3	0
TACE	14.3	58.6	0	0
Chemotherapy	47.6	7.3	45.5	45.5
Radiation	0	0	0	0
Tumor characteristics				
GTV (cm^3)				
median (range)	334.2 (9.5–1493.8)	(3–1913)	80.2 (30.6–818.5)	(10–465)
Number of lesions (%)				
1 lesion	76.2	79.8	81.8	100
>1 lesion	23.8	19.4	18.2	0
Metastatic (%)	9.5	2.7	45.5	83.3
SBRT				
Total dose (Gy)				
median (range)	30 (18–50)	(14–60)	30 (22–50)	(28.2–65)
Number of fractions	(1–10)	(1–12)	(1–10)	(3–6)
EQD2				
median (range)	50 (30–94)	–	70 (33–100)	–
Isodose line (%)				
median (range)	70 (60–75)	(65–95)	70 (65–70)	(65–80)

CC, Cleveland Clinic; GTV, gross tumor volume; Gy, grey; HCC, hepatocellular carcinoma; ICC intrahepatic cholangiocarcinoma; MSK, Memorial Sloan-Kettering; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; UHCMC, University Hospitals-Case Medical Center; URMC, University of Rochester Medical Center.
†references [13,17,22,23,26–28,30,31,34]; ††references [13,15,17,29,34]

of 70%. Previous treatments included systemic chemotherapy (47.6%), TACE (14.3%), RFA (4.8%) and liver resection (9.5%). Patients with ICC consisted in six men and five women with a median age of 66 years. Eighty one point eight percent of the patients had a single lesion while 18.2% were multicentric and 45.5% of patients presented with distant metastases. The median GTV was 80.2 cm^3 (range, 30.6–818.5), and median total prescribed dose was of 30 Gy in a median of 3 fractions with a similar isodose line of 70%. Prior treatments included systemic chemotherapy (45.5%), RFA (27.3%) and liver resection (50%).

The median follow-up for the HCC group was 12.9 months with an overall FFLP of 63.2% (Table II). The median time for local progression was 6.3 months with estimated rates of FFLP at six-months and one-year of 83% and 64%, respectively (Figure 1). Median OS was 34 months and the estimated one-year and two-years OS were 87% and 55%, respectively (Figure 2). Follow-up imaging studies to evaluate local response by RECIST criteria were available in 19/21 patients. Overall responses were: CR 10.5%, PR 15.8%, SD 31.6% and PD 42.1%. Median tumor volume decreased from an initial 334.2 cm^3 to a final volume of 135 cm^3, three months after treatment ($p = 0.004$, two-sided paired t-test, see Figure 3). Partial tumor responses were further graded as grade 1 response in 25% of tumors, grade 2 in 16.7% and grade 3 in 58.3% of the growths. Tumor recurrence was observed in 42.1% of patients. While the majority of patients (31.6%) had grade 1 recurrences (tumor progression within or at the periphery of the radiation field), 10.5% presented with grade 4 recurrences (combination of local and distant recurrences, Table II).

The median follow-up for the ICC group was 7.8 months (range, 1.4–17.9) with an overall FFLP of 55.5%. Median time to local progression was 4.3 months with estimated rates for FFLP at six-months and one-year of 63% and 50%, respectively (Figure 1). Median OS was 11 months and the estimated six-months and one-year OS were 75% and 45%, respectively (Figure 2). Patient with ICC had CR in

Table II. Survival data, tumor response and recurrence of malignancy of patients with non-resectable primary liver tumors treated with SBRT.

	HCC		ICC	
	Current series	Literature†	Current series	Literature††
Number of patients	21	224	11	16
Median FU (range, months)	12.9 (0.5–54)	(1–54)	4.8 (1.4–17.9)	(8–48)
Median overall survival (months)	34	(11.7–32)	11	(8–48)
1 year survival (%)	87	71	45	58
2 year survival (%)	55	48	–	–
3 year survival (%)	27	44	–	–
Overall freedom from local progression (%)	63.2	74	55.5	100
Median time to local progression (range)	6.3 (3.2–14.8)	–	4.2 (2.1–6.4)	–
RECIST (%,*)				
CR	10.5	34.9	11.1	–
PR	15.8	18.1	22.2	–
SD	31.6	11.2	22.2	–
PD	42.1	41.2	44.4	–
Partial tumor response grade (%,**)				
Grade 1	25	–	25	–
Grade 2	16.7	–	25	–
Grade 3	58.3	–	0	–
Tumor recurrence (%,***)				
Grade 1a	10.5	7.7	22.2	–
Grade 1b	21.1	16.5	11.1	–
Grade 2	0	10.3	11.1	–
Grade 3	0	12.9	0	–
Grade 4	10.5	14.3	22.2	–
Overall	42.1	61.7	66.7	–

CR, complete response; FU, follow-up; HCC, hepatocellular carcinoma; ICC intrahepatic cholangiocarcinoma; PD, progressive disease; PR, partial response; SBRT, stereotactic body radiotherapy; SD, stable disease.

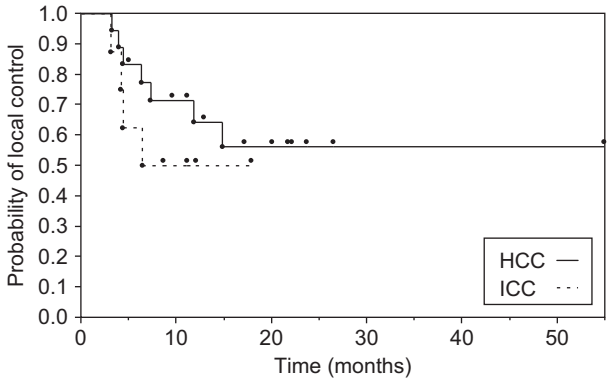
*Follow-up imaging data for RECIST was available only for 19 HCC and 9 ICC patients in our series and 92 HCC patients in the literature.

**Follow-up tumor volumes were available only for 12 HCC and 4 ICC patients in our series.

***Tumor recurrence data only available from 116 HCC patients in the literature.

†references [13,17,22,23,26–28,30,31,34].

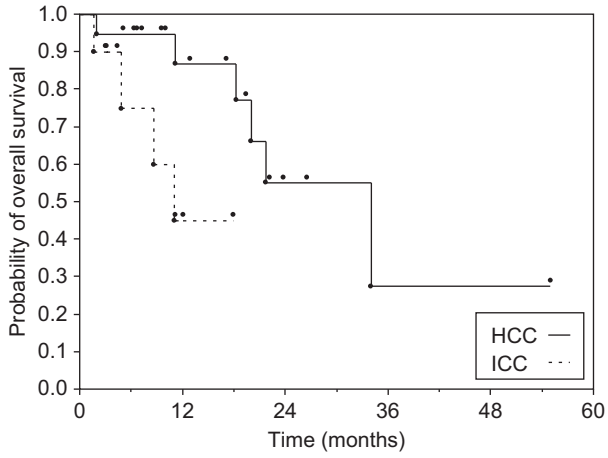
††references [13,15,17,29,34].



Number of patients at risk:

Time (months)	0	6	12	18	24
HCC	19	14	9	6	2
ICC	9	5	2	0	0

Figure 1. *Overall freedom from local progression (FFLP) in patients with primary liver tumors from the time of SBRT treatment*. The median time to local progression for patients with HCC was 6.3 months (range: 3.2–14.8 months). FFLP rates at 6-months and 1-year were 83 and 64%. The median time to local progression for patients with ICC was 4.3 months (range: 3.1–6.4 months). FFLP rates at 6-months and 1-year were 63 and 50%.



Number of patients at risk:

Time (months)	0	6	12	18	24
HCC	22	17	11	9	3
ICC	11	5	1	0	0

Figure 2. *Overall survival (OS) of patient with primary liver tumors from the time of SBRT treatment*. The median OS for patient with HCC was 34 months. The estimated 1-year and 2-years survival rates were 87 and 55%, respectively. The median OS for patients with ICC was 11 months. The estimated 6-months and 1-year survival rates were 75 and 45%, respectively.

11.1% three months after SBRT, PR in 22.2%, SD in 22.2% and PD in 44.4% of the cases. Although there was not a significant change in GTV three months after SBRT treatment, there was a decreased enhancement in MRI and PET scan images. Partial tumor responses were found as grade 1 response in 25% of tumors, grade 2 in 25% and no grade 3 responses. Tumor recurrence was observed in 66.7% of patients. Thirty three point one percent of them only presented grade 1 recurrence, 11.1% presented grade 3 recurrence and 22.2% presented grade 4 recurrences (Table II).

Adverse events

No adverse events from fiducial placement were noted. The overall incidence of Grade 1 and 2 radiation induced toxicities were 39.5%, most commonly presenting as nausea and fatigue. Grade 3 and 4 radiation induced toxicities were found in two and one patients, respectively. No grade 5 toxicities were present. The radiation induced adverse events rate by tumor type in our series and in the available literature are presented in Table III.

Discussion

Advanced primary liver tumors are a lethal condition with limited treatment options. Malignancy localized only in the liver may benefit from local therapy which can potentially achieve down-staging with a possibility for a definitive surgical therapy. The present studies showed that patients with non-resectable primary liver tumors (HCC/ICC) had a high FFLP rate of their disease (63.3/55.5%) and a relatively high overall survival at one year (87/45%). SBRT is an encouraging treatment modality with a low incidence of severe side effects (7–8%, grade ≥ 3) and clinical outcomes comparable to other non-surgical treatment therapies, such as RFA, PEI and TACE. These other modalities have shown rates of local control of 59–98.3% using RFA for tumors <5 cm diameter [5], 52% using PEI for

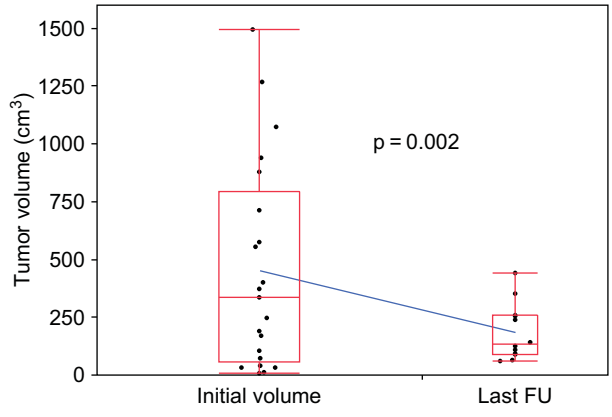


Figure 3. Box plot of *tumor gross tumor volume (GTV) response in patients with non-resectable HCC treated with SBRT.* GTV decreased from an initial median of 334.2 cm^3 to a final median of 135 cm^3 at 3 months follow-up ($p = 0.002$, two-sided paired t-test), follow-up data available for 19 patients in our series.

Table III. Radiation induced adverse events* reported in patients with non-resectable primary liver tumors treated with SBRT.

	HCC		ICC	
	Current series	Literature†	Current series	Literature††
Number of patients	21	224	11	16
Adverse events (%)				
Grade 1	25	32	28	33
Grade 2	5	26	21	33
Grade 3	4	10	7	17
Grade 4	4	2	0	0
Grade 5	0	0.4	0	0

HCC, hepatocellular carcinoma; ICC intrahepatic cholangiocarcinoma; SBRT, stereotactic body radiotherapy.
*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v3.0).
† references [13,17,22,23,26–28,30,31,34] data available for 173 patients.
††references [13,15,17,29,34] events data available for 12 patients.

tumors ≤ 2 cm diameter [6] and a recent meta-analysis of TACE for unresectable HCC reported 20–90% tumor response $\geq$SD with a reported duration of FFLP of 2–12 months [7]. In addition, the non-invasive nature of this modality makes it an attractive alternative for patients with severe medical conditions.

The initial report on SBRT for HCC was on nine patients treated in Sweden with 15–45 Gy in 1–3 fractions. Isocenter doses varied from 17 to 79 Gy (mean = 34 Gy). They achieved 100% FFLP at one year follow-up. Adverse events included nausea and fever although two patients had liver failure [13]. The National Defense Medical College of Japan published during the same year (1998) a series of 14 patients with HCC treated with SBRT who received 50 Gy in 2–12 fractions given at the 80% isodose line, obtaining 100% FFLP at two years follow-up with no significant adverse events [30]. Other series from Europe, Canada and Korea showed a FFLP rate for HCC between 65% and 93% at one year [17,24–26,28,32]. The group from Korea has treated a total of 68 patients with HCC, in their last analysis they excluded 15 patients with portal vein tumor thrombus, nine patients with large masses treated for palliative intent and two patients due to poor liver function. Although included patients had a GTV of ≤ 100 cm^3 (median of 15.4 cm^3 and range of 3–81.8 cm^3) their OS was 92.9 and 58.6% at one and three years, respectively, at a median follow-up of 28.7 months. Patients with tumors smaller than 32 cm^3 had better "in-field" progression free survival and OS rates, $p < 0.05$ [26]. The present study showed SBRT had similar rates of FFLP in advanced HCC stage when compared with published series of early HCC. The rate of radiation induced adverse events was comparable but the OS and the incidence of recurrences were higher in our study likely due to a more advanced malignant disease stage and higher degree of liver fibrosis at presentation.

Combination therapy was assessed in a series of 38 patients with HCC treated with TACE prior to SBRT. Median tumor volume was 40.5 cm^3 (range, 11–464 cm^3). Patients had an overall FFLP rate of 42.1% with a median survival of 32 months. Their OS was similar (42.1%) at three years. Only one patient presented grade 3 toxicity, six months after SBRT in the form of radiation dermatitis [31]. Recent series from Belgium, Hong Kong and from the University of Indiana showed patients treated by SBRT had a rate of FFLP between 87% and 95% at one year follow-up and a survival rate between 62% and 79% at one year [22,23,27]. Twenty-three patients from the Indiana University study underwent liver transplant at a median time of seven months. The rates of FFLP, progression free survival and OS in the transplanted group were 100%, 69% and 96%, respectively, at two-years. Only two patients developed distant metastasis [22]. The role of SBRT as primary therapy or as adjuvant or neo-adjuvant treatment for HCC still remains to be determined.

Only 10% to 20% of cholangiocarciomas are ICC. Surgical approaches for ICC are often ineffective due to high rates of disease recurrences, late presentation or multifocal behavior. Regional therapies for ICC are more limited than for HCC due to the intraluminal growth along the segmental pedicles and the lack of predominant vascular inflow. Published series are very limited in number of treated patients, specific data and their follow-up. University of Toronto phase I study on SBRT for primary liver tumors in 2008 included 10 ICCs. The median GTV was 172 cm^3 (range, 10–465 cm^3) and all patients had vascular involvement or extrahepatic disease at baseline. OS was 58% at one-year [17]. Other published series of primary liver tumors from Sweden and Germany included each one a single ICC case and they reported 100% FFLP at last follow-up (11 months in one patient, not specified in the other)

[13,34]. Finally, a single case report from Korea (2010) treated a 3.5×4.0 cm ICC with chemoradiation. They used three cycles of S-1 as a radiosentitizer followed by SBRT (45 Gy in 5 fractions delivered with the CyberKnife® system) and followed by nine additional cycles of S-1. They reported no signs of tumor progression, distant metastasis or death at eight months follow-up [29]. The present study showed SBRT treatment for ICC had high rates of FFLP but also high rates of distal recurrences. SBRT may have a role in the adjuvant treatment of ICC or as part of a multimodality therapy for non-resectable ICC.

We have not attempted a dose response study in our patients since the number of subjects available for enrollment is small. Some studies described a dose response for patients with liver and lung tumors undergoing SBRT [37] and for patients with liver metastasis [38,39]. The FFLP in our treated patients were not significantly different at the dose prescribed with lower side effects when compared with the literature. However, in the present study we are working with relatively larger tumors. The frequency of primary liver tumors amenable to SBRT is low and meaningful dose response curves will take several years to validate even within a multi-institutional approach.

SBRT is a safe and effective option for the treatment of primary liver tumors. Selection of patients is important to achieve desirable outcomes in a multidisciplinary approach; non-metastatic and smaller tumors have shown to be associated with better responses and long-term control of the disease [26]. We proposed considering SBRT as an option for the down-staging of HCC in patients beyond Milan criteria [19]. Others had made SBRT their primary bridging option for HCC patients in the transplant list and one of the first options for non-transplantable patients [22]. SBRT may be offered early in patients with inoperable HCC as a multimodal treatment approach.

Conclusions

Stereotactic body radiotherapy is a promising local treatment modality for the treatment of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. It had showed a low incidence of severe side effects with fairly good rates of freedom from local progression. Randomized controlled trials are needed to further define the role of SBRT in the treatment of primary liver tumors.

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