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Stereotactic Body Radiation Therapy as an Alternative to Transarterial Chemoembolization for Hepatocellular Carcinoma

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Abstract

Purpose—To conduct a large single-institution comparison of transarterial chemoembolization (TACE) and stereotactic body radiation therapy (SBRT) outcomes in similar groups of patients with hepatocellular carcinoma (HCC).

Methods and Materials—From 2006 to 2014, 209 patients with 1 to 2 tumors underwent TACE (n=84) to 114 tumors or image guided SBRT (n=125) to 173 tumors. Propensity score analysis with inverse probability of treatment weighting was used to compare outcomes between treatments while adjusting for imbalances in treatment assignment. Local control (LC), toxicity, and overall survival (OS) were retrospectively analyzed.

Results—The TACE and SBRT groups were similar with respect to the number of tumors treated per patient, underlying liver disease, and baseline liver function. Patients treated with SBRT were older (65 vs 61 years, P=.01), had smaller tumors (2.3 vs 2.9 cm, P<.001), and less frequently underwent liver transplantation (8% vs 18%, P=.01). The 1- and 2-year LC favored SBRT: 97% and 91%, respectively, for SBRT and 47% and 23% for TACE (hazard ratio 66.5, P<.001). For patients treated with TACE, higher alpha-fetoprotein (hazard ratio 1.11 per doubling, P=.008) and segmental portal vein thrombosis (hazard ratio 9.9, P<.001) were associated with worse LC.

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Predictors associated with LC after SBRT were not identified. Grade 3+ toxicity occurred after 13% and 8% of TACE and SBRT treatments, respectively (*P*=.05). There was no difference in OS between patients treated with TACE or SBRT.

Conclusions—Stereotactic body radiation therapy is a safe alternative to TACE for 1 to 2 tumors and provides better LC, with no observed difference in OS. Prospective comparative trials of TACE and SBRT are warranted.

Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of cancer death worldwide, and its incidence has continuously risen in the last few decades (1, 2). Liver transplantation and surgical management are preferred, but not all patients are suitable. Liver-directed regional arterial (eg, transarterial chemoembolization [TACE] or radioembolization) and ablative therapies (eg, radiofrequency ablation [RFA], microwave ablation, stereotactic body radiation therapy [SBRT]) are commonly applied therapies designed to achieve local control (LC) or bridge patients to liver transplantation (3–7). Transarterial chemoembolization is the most commonly administered liver-directed therapy for patients with unresectable HCC. Although the Barcelona Cancer Liver Cancer (BCLC) staging classification and treatment algorithm recommends reservation of chemoembolization for intermediate stage B, it is often used worldwide in patients with a limited number of liver lesions (8–14). Stereotactic body radiation therapy is a newer treatment modality with evidence of promising LC in HCC patients (15–17). A previous study found that SBRT compared favorably to RFA (17). However, there have been no comparative studies to date between TACE and SBRT. In this study we summarize our institutional experience with the hypothesis that SBRT provides comparable or better LC compared with TACE in patients with up to 2 liver HCC tumors, with similar overall survival. We also studied patient- and tumor-related factors that may predict for local failure after TACE or SBRT.

Patients and Methods

Data collection, modality selection

After institutional review board approval, HCC patients receiving liver SBRT from 2006 to 2014 at our institution were identified from a prospective departmental database. Patients treated with TACE between 2007 and 2014 were identified in an institutional cancer center database. Data abstraction was supported with the Electronic Medical Record Search Engine (EMERSE) registry (18) using Current Procedural Terminology, 4th edition codes (36245, 36260, 37242, 37243, 75894, and 75896), International Classification of Diseases (ICD)-9 codes (155.0, 155.2), and ICD-10 codes (C22.0-C22.9). To aid in meaningful comparisons, this study was limited to patients with nonmetastatic HCC who received treatment with TACE or SBRT to 1 to 2 liver concurrent tumors and did not receive previous or concurrent sorafenib. Patient and tumor characteristics, treatment details, and clinical outcomes were collected from medical records. Treatment recommendations were made at our institutional multidisciplinary liver tumor board, following National Comprehensive Cancer Network guidelines. This weekly tumor board has had relatively stable membership over the past

decade and is attended by hepatobiliary surgeons, liver transplant surgeons, hepatologists, radiation oncologists, interventional radiologists, medical oncologists, abdominal radiologists, and a pathologist. Overall TACE was typically preferred for patients who were thought to be eligible for future liver transplantation and had multiple liver tumors too large for RFA. Stereotactic body radiation therapy was generally reserved for patients with tumors that progressed after TACE or RFA, patients unsuitable for RFA, or patients with very large tumors or poor liver function. Additionally, interventional radiology generally followed standard criteria for liver function when deciding on appropriateness of TACE (19), and radiation oncology followed previously published toxicity models, limited to 15% risk of liver damage, to determine appropriate candidacy (20). Eastern Cooperative Oncology Group (ECOG) performance status was longitudinally assessed prospectively by the treating physician for patients who received SBRT and estimated on the basis of available history and physical examination descriptions for all other patients.

TACE treatments

Catheter chemoembolization was performed by interventional radiologists in the angiography suite under sedation using standard techniques. All patients received antibiotic prophylaxis coverage. Arterial anatomy relevant to tumor supply was identified on preprocedural cross-sectional imaging. Celiac and superior mesenteric arteriography was performed through 5-French (Fr) base catheters with standard digital subtraction angiography to confirm and map out tumor arterial supply. Once mapping was sufficient, a coaxial 2.4-Fr microcatheter was advanced subselectively into the hepatic artery branch afferent to the tumor-bearing hepatic segment. When technically feasible, the microcatheter was advanced into a subsegmental branch supplying the tumor. Accessory or additional arteries apparent after initial embolization were also catheterized and embolized separately for complete tumor coverage.

From 2006 to 2008, conventional triple agent TACE was typically performed, using cisplatin, doxorubicin, and mitomycin-C. Our institutional protocol used 100 mg cisplatin (Bristol Myers Squibb, Princeton, NJ), 50 mg doxorubicin (Pharmacia Upjohn, Kalamazoo, MI), and 10 mg mitomycin (Bedford Laboratories, Bedford, OH), reconstituted in 10 mL nonionic contrast material (Omnipaque 300, Winthrop Pharmaceuticals, New York, NY). The mixture was emulsified in 8 to 10 mL ethiodized oil (Lipiodol Ultra-Fluide, Guerbet, Bloomington, IN) and delivered through the microcatheter to all branches afferent to the tumor. Delivery was performed under fluoroscopic guidance and followed by additional branch vessel embolization using 100- to 500-μm tris-acryl microspheres (Embospheres, Merit Medical Systems, South Jordan, UT) to an endpoint of near stasis on fluoroscopy.

From 2009 to 2014, drug-eluting bead TACE (DEB-TACE) was typically performed. This consisted of injection of 2 to 4 mL LC Beads 100 to 300 or 300 to 500 μm (AngioDynamics, Lathan, NY) loaded with doxorubicin (50–75 mg) for a total dose per session of 50 to 150 mg doxorubicin. Total dose was dictated by embolization endpoint. The beads were mixed with a volume of nonionic contrast medium, normal saline 1:3 for a 20-cm^3 total volume, delivered at 1 cm^3/min. After chemoembolization with conventional or DEB-TACE, arteriography showed patency of proximal first- and second-order hepatic artery branches.

SBRT treatments

After immobilization in the supine position with a customized vacuum body mold, patients underwent contrast-enhanced computed tomography (CT) simulation. To account for breathing-related tumor motion, an active breathing control device or spirometric motion management system was used. If patients could not tolerate breath-hold, 4-dimensional CT was used to generate an internal target volume. For optimum tumor delineation, pretreatment magnetic resonance images were fused with simulation scans (21). The gross tumor volume or internal target volume was expanded by 5 mm radially and 8 mm craniocaudally for the planning target volume (PTV) (22). Stereotactic body radiation therapy was planned using 3-dimensional conformal techniques generally with 8 to 12 non-opposed, non-coplanar static 6- and 16-MV beams. Radiation dose was prescribed to the isodose surface covering 99.5% of the PTV, typically 75% to 85% of maximum PTV dose. Patients received either 3 or 5 fractions (50% each), delivered every other day. Assuming an α/β ratio of 10, the median biologically equivalent dose for all patients was 100 Gy. Dose limits to 0.5 cm^3 of the duodenum, stomach, and heart were 30 Gy, 27.5 Gy, and 52.5 Gy, respectively, whereas <30 cm^3 of the chest wall was permitted to receive ≥35 Gy for patients treated with 5 fractions. If the treatment was delivered in 3 fractions, dose limits were 24 Gy, 22.5 Gy, 30 Gy, and 30 Gy, respectively.

Positioning and image guidance was performed daily with either orthogonal X-rays or cone beam CT imaging. X-ray alignment was performed for up to 3 percutaneously placed intrahepatic fiducial markers in or near the treated tumor, whereas cone beam CT alignment included either fiducial markers or adjacent landmarks, such as large liver vessels, and individual parenchymal characteristics of the treated portion of the liver.

Follow-up

Clinical evaluation, liver function testing, and imaging with liver CTor magnetic resonance imaging were performed 8 to 12 weeks after completion of SBRT or TACE, then every 3 months. Adverse events were defined as grade ≥3 events according to National Institutes of Health–defined Common Terminology Criteria for Adverse Events during the 30 days after treatment (acute) or at any other time (late biliary and luminal gastrointestinal [GI] toxicity). Radiological and clinical findings of patients with suspected disease progression after initial treatment were reviewed at a multidisciplinary liver tumor board with diagnostic and interventional radiologists, pathologist, surgeons, and medical and radiation oncologists; for local, in-liver, or extrahepatic progression, additional therapy with TACE, RFA, SBRT, radioembolization, or sorafenib was recommended. Freedom from in-liver progression (FFLP) was defined as time from treatment until first treatment failure anywhere in the liver, including locally. Freedom from new liver tumor refers to time from treatment until appearance of new lesion(s) in the liver. Local control was defined as absence of progressive disease by Response Evaluation Criteria in Solid Tumors within or at the tumor margin for patients receiving SBRTand within or adjacent to the embolization cavity for patients receiving TACE. For patients treated with radiation therapy, treatment plans were compared with subsequent imaging to determine whether growing tumors were local recurrences or untreated tumors. For TACE patients, similar comparisons were made with procedural images and/or radiology reports. In patients treated with TACE, tumors requiring multiple

embolization procedures because of residual disease were not counted as failures. Pathologic response data in patients treated with liver transplantation after TACE or SBRT were collected from postoperative pathology reports.

Statistics

The TACE and SBRT groups were compared at both patient and tumor levels. *T* tests, Wilcoxon Mann-Whitney tests, *z* tests, and χ^2 tests were used for normal variables, ordinal but nonnormal variables, 2-sample proportions, and nominal categorical variables, respectively. Local control and FFLP were calculated at the tumor level as time from treatment initiation to subsequent local progression, liver transplant, or last follow-up. Overall survival was calculated at the patient level as the time from first treatment (with TACE or SBRT) to death (from any cause) or last follow-up. The effect of treatment and other covariates on LC was modeled using a mixed-effects Cox model with patient-level random effects to adjust for correlation between tumors of the same patient (23). We applied inverse probability of treatment weighting (IPTW) to the Kaplan-Meier method and Cox models for LC to adjust for potential treatment assignment imbalances (24). The treatment probabilities (ie, propensity) were calculated, at the tumor level, from a logistic regression using a set of covariates likely to have affected original treatment decisions, including referring physician, age, number of liver tumors, tumor size, performance status, and number of prior treatments. All of these variables were included, regardless of statistical significance. To avoid extreme weights, we truncated the estimated propensities by the 5th and 95th percentiles. We conducted univariate analysis using either the treatment-only model or models that included 1 covariate and the treatment indicator. We also conducted multivariate analysis for treatment and covariates altogether. Analyses were performed using R (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 209 patients with 287 HCC tumors were identified, of whom 84 patients with 114 liver tumors were treated with TACE and 125 patients with 173 tumors were treated with SBRT (Table 1). Seventeen patients were treated with TACE and SBRT to different tumors, and 1 patient had resection of a separate tumor as part of overall management. Patients treated with TACE were younger (60.8 vs 65 years, $P<.01$), had slightly larger tumors (2.9 cm vs 2.3 cm, $P<.001$), more active tumors at the time of treatment (median 2 vs 1, $P<.001$), and worse ECOG performance status (ECOG ≥2 33% vs 11%, $P<.001$) than patients managed with SBRT. Patients treated with TACE received fewer prior liver-directed treatments, including surgical resection, RFA, SBRT, conventional radiation therapy, TACE, and radioembolization (median 0 vs 2, $P<.001$) than patients treated with SBRT, and were more often treated with liver transplantation (18.4% vs 8.7%, $P=.01$). The median time from primary diagnosis date to treatment date was shorter for TACE compared with SBRT ($P<.001$): 2.2 months (range, 0.4–37.2 months) versus 7.1 months (range, 0.5–104.9 months). Median follow-up was longer for patients treated with TACE (23.0 vs 12.4 months, $P<.001$). Seventeen patients (9%) were treated with both TACE and SBRT for different tumors but not to the same tumor. To correct for potential imbalances in treatment assignments, we

performed IPTW analysis. After applying the propensity weights, there were no longer significant differences between SBRT and TACE patients.

LC, FFLP, overall survival, and pathological response rates

Unadjusted 1- and 2-year LC rates were 96.5% and 91.3%, respectively, for patients treated with SBRT, compared with 47.1% and 22.9% for patients with TACE (Fig. 1). Patients needed more additional liver-directed treatments (68% vs 34%, $P<.001$) and systemic therapy (16.7% vs 6.4%, $P=.01$) after TACE compared with SBRT. After IPTW, in univariate analysis, treatment modality was a significant predictor of local progression (hazard ratio [HR] 15.7, $P<.001$ for TACE vs SBRT; Table 2). After adjusting for treatment type, segmental portal vein (PV) thrombosis (HR 8.67, $P<.001$) and high alpha-fetoprotein (AFP) (HR 1.1 per doubling, $P=.01$) were the only covariates associated with local progression for all patients. Age, size, number of previous liver-directed therapies, baseline liver function (Child-Pugh score), and ECOG performance status were not associated with local progression.

When treatment modalities were analyzed separately, segmental PV thrombosis and AFP remained significant predictors for local progression after TACE (HR 9.93, $P<.001$, and HR 1.11 per doubling, $P=.008$, respectively) but not after SBRT (HR 3.39, $P=.34$, and HR 1.03, $P=.87$). In patients managed with SBRT, no proposed factor, including PV thrombosis, AFP, use of fiducials, higher total dose, and enrollment on a clinical trial, affected local progression. For patients treated with TACE, there was no difference in LC between conventional and DEB-TACE, large (≥300 μm) versus small (<300 μm) beads, and number of TACE treatments. On multivariate analysis, treatment with TACE, older age, high pretreatment AFP, presence of minor PV branch thrombosis, and previous treatment of that tumor were predictive of local failure (Table 3).

The FFLP rates at 1 and 2 years (Fig. 2) were lower for patients after TACE than after SBRT (35.9% and 10.7% vs 56.5% and 26.9%, respectively), with overall FFLP significantly favoring SBRT (HR 3.55, 95% confidence interval 1.94–6.52, $P<.001$). On multivariate analysis TACE treatment, high pretreatment AFP, minor PV branch thrombosis, and previous treatment of that tumor were significant covariates associated with FFLP (Table 4). When local progression was excluded from the analysis of FFLP, freedom from new liver tumor in patients treated with TACE versus SBRT was not different (HR 0.71, $P=.25$).

Overall survival at 1 and 2 years was 75.3% and 54.9%, respectively, after TACE and 74.1% and 34.9% after SBRT, with no significant difference between treatment groups after adjustment for age, Child-Pugh score, baseline cirrhosis, liver transplantation, time from diagnosis of HCC, and thrombosis of minor branches of PV (HR 0.76, $P=.21$).

At the time of liver transplantation, pathologic complete response was identified in 7 out of 12 evaluable lesions (58%) after SBRT and in 5 out of 21 assessable tumors (24%) after TACE ($P=.054$) using Fisher’s exact test.

Adverse events

Overall, more grade ≥3 adverse events occurred in patients after TACE than after SBRT (13% and 8%, respectively, P=.05). Eleven were observed in the TACE group, including severe hypervolemia after TACE (n=3), acute cholecystitis (n=2), severe anasarca associated with hypovolemic renal failure (n=1), biliary abscess (n=1), hepatic artery injury (n=1), biliary stricture (n=1), upper GI bleeding caused by gastric ulcer (n=1), and severe hyperkalemia with a non-ST-elevated myocardial infarction immediately after TACE (n=1). No deaths occurred within 1 month of treatment. In the SBRT group, 10 grade ≥3 acute toxicities were observed: biliary strictures (n=4), upper GI bleeding associated with gastric or duodenal ulcer (n=3), bleeding from esophageal varices (n=1), and severe hypervolemia after SBRT (n=1). One patient developed radiation induced liver disease.

Discussion

In this study, SBRT provided substantially better LC than TACE. Neither SBRT nor TACE seemed to prevent development of new tumors elsewhere in the liver. Thus, SBRT provided better overall in-liver control and higher potential cure rates, without compromising safety or overall survival. Additionally, acute toxicity was more common after TACE, owing to procedural invasiveness.

Transcatheter arterial chemoembolization is widely used in the management of unresectable HCC. According to BCLC guidelines it should be reserved for patients with good performance status, Child-Pugh A-B liver function, and intermediate-stage multinodular HCC. However, it is commonly applied to patients with early-stage HCC of up to 3 nodules <3 cm and, in many institutions, patients with solitary small tumors, particularly if not amenable to RFA. Stereotactic body radiation therapy is a newer treatment that delivers precise, high-dose ablative radiation. Although not yet incorporated into the BCLC algorithm, SBRT is a locoregional therapy option in the National Comprehensive Cancer Network hepatobiliary cancer guidelines, along with ablation and arterially directed therapies. Currently there is a paucity of comparative data for different forms of local and regional therapy. A recent retrospective study by Wahl et al (17) suggests that LC rates after SBRT and RFA were overall similar, but local failures in HCC lesions larger than 2 cm were more common after RFA. There was no difference in overall survival according to treatment modality (17). In another retrospective study from the University of Toronto assessing the effectiveness of bridging therapy for transplant, SBRT, RFA, and TACE were found to have similar tumor necrosis at explant, transplant dropout rates, postoperative complications, and overall survival. However, all patients examined in this study were on the transplant list before treatment, and thus more than 80% of patients went on to transplant (25). Nontransplant candidates need longer-term tumor control, and thus local and in-liver tumor control are of increased importance.

Tumor control rates after TACE have been quite variable, even in prospective studies (26–28). In a recently published study (29), up to 40% of patients treated with DEB-TACE were responders 3 months after therapy. However, data on LC in patients with a limited number of HCC tumors are scarce, and comparison with previously published series is difficult, owing to differences in the definition of local progression. Brown et al (29) report a 12% response

rate in patients after DEB-TACE at 12 months. In prior series, the long-term LC rate after TACE has ranged from 23% to 35% (11, 12, 30). This is consistent with our results with meticulous review of longitudinal scans, focusing on treated tumors and application of Response Evaluation Criteria in Solid Tumors. Our LC rate with SBRT compares favorably to the published literature. In the largest prospective study to date, the 2-year LC rate was reported as 74% (15). Smaller retrospective studies show rates of LC in a range of 84% to 92% (31–33). Thus, given the agreement with prior literature, the higher rate of LC after SBRT in this study is most likely due to a true difference in the treatment effectiveness, rather than an artifact from particularly excellent SBRT or poor TACE.

Our findings still need to be verified prospectively. Currently 2 randomized phase 2 trials are recruiting patients: NCT02182687 targets patients within Milan Criteria eligible for orthotopic liver transplantation. The study is designed to compare TACE or SBRT as a bridge to transplant with the primary outcome time to first additional intervention. NCT02470533 targets patients with 1 to 3 tumors and assesses time to any progression after DEB-TACE or after SBRT. These studies are not anticipated to be published before 2019 and 2020, respectively, if accrual continues on schedule. Thus, the results of this study are important interim data for SBRT in patients who may be eligible for TACE.

Unfortunately, currently there are no treatments other than liver transplant that can effectively prevent development of HCC elsewhere in the liver (34–36). In recent years there have been several reports on the combination of TACE and SBRT, suggesting that the combination may yield better outcomes than TACE alone (37–39). However, given the excellent tumor control rate from SBRT alone in our study, and modest in-liver control from TACE, combining TACE with SBRT may not improve tumor outcomes and potentially could increase the risk of treatment-related adverse events. The likely reason that TACE does not outperform SBRT outside the target lesion is that, for early HCC, the tumor receives additional blood supply from the portal system (40, 41). Prospective trials comparing combined SBRT and TACE treatment to SBRT alone are warranted.

Several limitations are inherent in the present study owing to its retrospective nature and relatively short follow-up. In addition, although patient characteristics were well balanced in many aspects between the 2 treatment groups, some characteristics favored SBRT and others favored TACE. We adjusted for these imbalances using inverse probability of treatment weighting, but we cannot rule out unmeasured confounding, which could result in subtle biases. Additionally, shorter follow-up for patients with SBRT may underestimate long-term side effects, although our acute toxicity rates are similar to those in published studies. Overall survival, although not statistically significant, was numerically lower at 2 years after SBRT; it is unclear whether this is due to remaining imbalances in treatment groups even after IPTW, or whether it is related to therapy.

In conclusion, the results of our study suggest that SBRT is a safe treatment for patients with 1 to 2 HCC tumors and generates superior LC and in-liver control when compared with TACE. These findings highlight the need for results from ongoing randomized trials comparing TACE with SBRT and suggest that in the absence of such data, SBRT is an alternative treatment for patients with 1 or 2 HCC tumors.

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Summary

Few comparative data exist to help guide nonsurgical treatment selection for patients with hepatocellular carcinoma. Thus, we compared the effectiveness and toxicity of transarterial chemoembolization and stereotactic body radiation therapy (SBRT) and found both to be superior with SBRT. This can inform future prospective trial design.

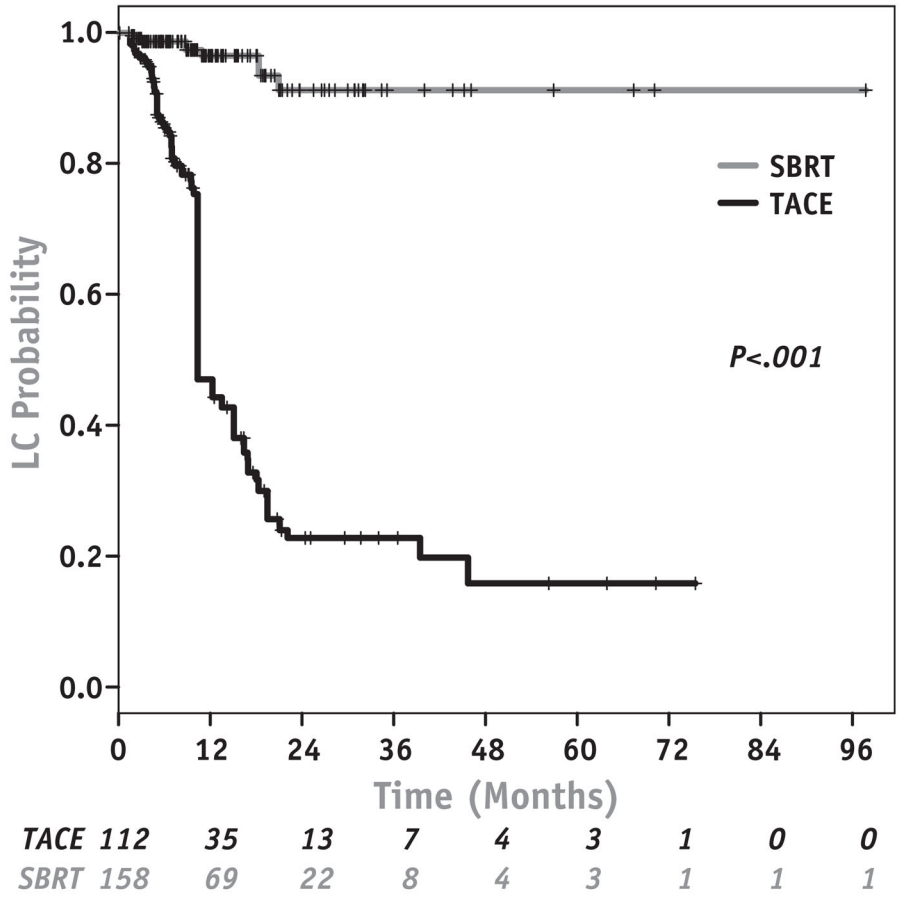

Fig. 1.

Local control (LC) by treatment modality. *Abbreviations:* SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization.

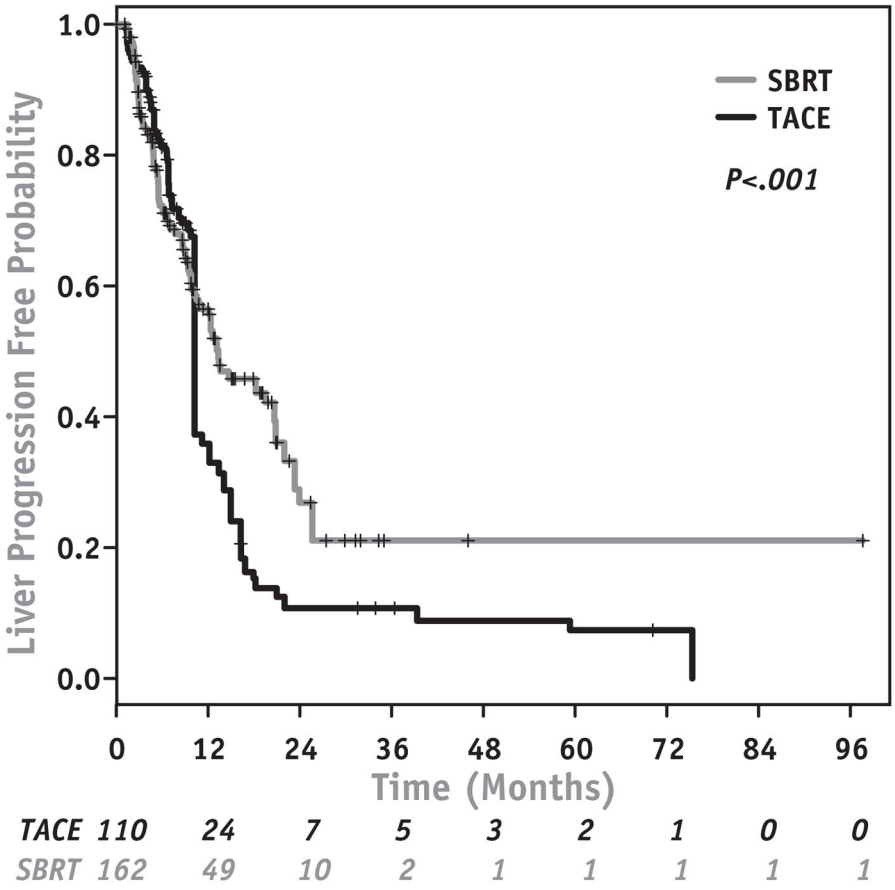

Fig. 2.

Freedom from in-liver progression by treatment modality. *Abbreviations:* SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization.

Table 1

Patient, tumor, and treatment characteristics

Characteristic	Before IPTW			After IPTW		
	TACE	SBRT	*P*	TACE	SBRT	*P*
No. of patients	84	125				
Age (y)			.01			.75
Median	60.8	65.0		62.1	61.8	
Range	46.2–83.2	25.9–86.2		46.2–83.2	25.9–86.2	
Sex, male	68 (81.0)	102 (81.6)	.91	76 (78.7)	85 (75.7)	.63
ECOG score			<.001			.15
<2	74 (66.6)	154 (89.0)		142 (85.5)	95 (79.2)	
≥2	37 (33.3)	19 (11.0)		24 (14.5)	25 (20.8)	
No. of tumors	114	173				
Tumor maximal diameter (cm)			<.001			.10
Median	2.9	2.3		2.7	2.4	
Range	0.7–15.0	0.0–20.8		0.7–15.0	0.0–20.8	
No. of active liver tumors at time of treatment			<.001			.09
Median	2	1		1	1	
Range	1–5	1–5		1–5	1–5	
Segmental portal vein branch thrombosis (yes)	8 (7.0)	20 (11.6)	.20	10 (6.0)	14 (11.7)	.10
AFP score			.43			.52
Median	17.5	14.0		12.0	15.0	
Range	2–23,150	2–16,260		2–23,150	2–16,260	
Liver disease			.50			.62
Hepatitis B	4 (3.5)	11 (6.4)		4 (2.5)	5 (4.3)	
Hepatitis C	65 (47.4)	85 (49.1)		71 (44.9)	56 (47.8)	
Alcoholic cirrhosis	18 (15.8)	42 (24.3)		40 (25.3)	29 (24.8)	
NAFLD	11 (9.6)	12 (6.9)		20 (12.7)	11 (9.4)	
Other	10 (8.8)	18 (10.4)		23 (14.6)	16 (13.7)	
Cirrhosis	97 (85.1)	148 (85.5)	.91	130 (77.8)	102 (85.0)	.13
Child-Pugh score			.19			.32

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2019 January 01.

Characteristic	Before IPTW			After IPTW		
	TACE	SBRT	*P*	TACE	SBRT	*P*
Median	6	6		6	6	
Range	5–9	5–9		5–9	5–9	
Liver transplant	21 (18.4)	15 (8.7)	.01	14 (8.4)	8 (6.7)	.59
No. of pretreatment liver-directed therapies			<.001			.30
Median	0	2		1	1	
Range	0–3	0–8		0–3	0–6	
DEB in TACE (yes)	87 (76.4)	-				
Beads >300 used	56 (49.1)					
Fiducials in SBRT (yes)	-	32 (18.5)				

Abbreviations: AFP = alpha-fetoprotein; DEB = drug-eluted beads; ECOG = Eastern Cooperative Oncology Group; IPTW = inverse probability of treatment weighting; NAFLD = non-alcoholic fatty liver disease; SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization.

Data are presented as number (percentage) unless otherwise noted. Only age and sex are on patient level; all other variables are on tumor level. All variables are at baseline (ie, time of treatment), unless otherwise noted.

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2019 January 01.

Table 2

Univariate analysis of variables predictive for local progression

	All tumors			TACE			SBRT		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Treatment: TACE vs SBRT	15.7	5.59–44.1	<.001	-		-	-		-
Age, per year	0.99	0.96–1.02	.63	1.02	0.96–1.08	.50	0.99	0.90–1.08	.76
ECOG, ≥2 vs <2	0.66	0.32–1.35	.26	0.69	0.25–1.90	.48	0.64	0.20–1.85	.58
Tumor maximal diameter, per cm	1.06	0.96–1.17	.23	1.08	0.96–1.21	.19	0.64	0.23–1.78	.40
Segmental portal vein branch thrombosis, yes vs no	8.67	3.68–20.4	<.001	9.93	4.02–24.6	<.001	3.39	0.28–40.6	.34
AFP	1.10	1.03–1.19	.01	1.11	1.03–1.20	.008	1.03	0.72–1.47	.87
Child-Pugh score	1.09	0.78–1.53	.60	1.15	0.74–1.78	.54	1.03	0.45–2.36	.94
No. of pretreatment liver-directed therapies	0.81	0.65–1.02	.07	0.77	0.61–0.98	.04	1.16	0.64–2.10	.63
Previous treatment to that tumor, yes vs no	0.78	0.46–1.34	.37	0.77	0.45–1.34	.36	1.01	0.12–8.27	.99
DEB for TACE, yes vs no	-		-	1.32	0.45–3.94	.61	-		-
No. of TACE treatments	-		-	0.76	0.41–1.41	.39	-		-
Bead size in TACE, ≥300 vs < 300	-		-	1.18	0.62–2.27	.61	-		-
SBRT on research protocol, yes vs no	-		-	-		-	0.96	0.13–7.20	.97
Fiducials, yes vs no	-		-	-		-	0.44	0.07–2.81	.39
SBRT total dose per Gy	-		-	-		-	0.95	0.86–1.05	.33

Abbreviations: CI = confidence interval; HR = hazard ratio. Other abbreviations as in Table 1.

Table 3

Multivariate Cox proportional hazards analysis of factors associated with local progression

Variable	HR	95% CI	*P*
Treatment, TACE vs SBRT	66.5	18.99–233.0	<.001
Age, per year	1.05	1.00–1.10	.05
ECOG, ≥2 vs <2	0.83	0.34–2.05	.69
Tumor size, per cm	1.00	0.89–1.13	.98
No. of pretreatment liver-directed therapies	0.70	0.46–1.08	.11
Previous treatment to that tumor, yes vs no	6.51	1.93–21.9	.003
Segmental portal vein branch thrombosis, yes vs no	14.7	4.34–49.8	<.001
AFP, per doubling	1.16	1.04–1.28	.006
Child-Pugh score	1.27	0.84–1.92	.27

Abbreviations as in Tables 1 and 2.

Table 4

Multivariate Cox proportional hazards analysis of factors associated with in-liver progression

Variable	HR	95% CI	*P*
Treatment, TACE vs SBRT	3.55	1.94–6.52	<.001
Age, per year	1.00	0.97–1.03	.99
ECOG, ≥2 vs <2	0.87	0.42–1.78	.69
Tumor size, per cm	0.98	0.89–1.08	.74
Previous treatment to that tumor, yes vs no	2.42	1.16–5.04	.02
No. of pretreatment liver-directed therapies	1.08	0.84–1.37	.55
Segmental portal vein branch thrombosis, yes vs no	4.58	1.92–10.9	.001
AFP, per doubling	1.15	1.06–1.24	.001
Child-Pugh score	1.04	0.78–1.39	.78

Abbreviations as in Tables 1 and 2.