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Better survival after stereotactic body radiation therapy following transarterial chemoembolization in nonresectable hepatocellular carcinoma: A propensity score matched analysis

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ABSTRACT

Background: This study compared outcomes of nonresectable hepatocellular carcinoma (HCC) who had transarterial chemoembolization (TACE) vs. stereotactic body radiation therapy (SBRT) after TACE (TACE + SBRT).

Methods: This was a retrospective study of 2 centers in Hong Kong. There were 49 patients who had TACE + SBRT and 202 patients who had TACE alone. Propensity score matching was used to adjust for differences in patients' demographics and tumor characteristics between the 2 groups. The primary outcome was overall survival (OS) and secondary outcomes were progression-free survival (PFS) and treatment-related toxicity.

Results: After matching, 49 patients were in the TACE + SBRT group and 98 patients in the TACE group with similar baseline characteristics. The 1-&3-year OS were better in TACE + SBRT group (67.2 vs. 43.9% and 36.5 vs. 13.3%, $p = 0.003$). The 1-&3-year PFS was also better in TACE + SBRT group (32.5 vs. 21.4% and 15.1 vs. 5.1%, $p = 0.012$). Radiological disease control was better in the TACE + SBRT group (98 vs. 56.7%). Risk of severe toxicity was uncommon in both treatment arms. TACE + SBRT was an independent good prognostic factor for OS and PFS in multivariate analysis, whereas AFP > 200 ng/ml, large tumor and multiple tumors predicted worse OS.

Conclusion: TACE + SBRT is safe and results in better survivals in nonresectable HCC patients.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world [1]. The incidence of HCC is increasing and most patients are diagnosed with intermediate/advanced disease and the cure rate is < 10% [2,3]. Transarterial chemoembolization (TACE) is the standard of care for intermediate stage HCC. A randomized controlled trial from our center in 2002 was one of the landmark studies to demonstrate the benefits of TACE [4]. Unfortunately, there is no major change in treatment strategy in nonresectable HCC patients since then. TACE is ineffective in patients with large tumor burden (i.e. tumor > 5cm/multifocal HCC) or cirrhosis [4,5]. Efforts were made to improve response to TACE such as with the use of drug-eluting beads or TACE followed by sorafenib, but none has demonstrated benefits consistently [6–8].

Until recently, conventional external radiation has a very limited role in the management of HCC because it was impossible to deliver high tumoricidal dose without causing radiation-induced liver disease (RILD) [9]. Stereotactic body radiation therapy (SBRT) refers to the use of a few fractions (usually < 10) of potent doses of highly conformal radiation therapy with high geometric precision and accuracy, thus being able to deliver a high tumoricidal dose to the tumor while

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limiting radiation to surrounding normal tissues. There were a few prospective series on SBRT in nonresectable HCC and showed an overall survival (OS) of 34–68.7% at 2-year and minimal RILD [10–13]. These promising early results suggested that SBRT might be a more powerful loco-regional treatment for nonresectable HCC. Combining TACE and SBRT (TACE + SBRT) might have synergistic effects [12,14–17]. In this study, we compared the outcomes of TACE + SBRT vs. TACE alone for nonresectable, nontransplantable and nonablatable HCC patients.

2. Materials and methods

This was a 2 centers retrospective study, at Tuen Mun Hospital and Queen Mary Hospital, the University of Hong Kong, Hong Kong. Data were retrieved from a prospectively collected database. This study was approved by institutional review board (UW18-428). From 2007, Tuen Mun Hospital started to provide SBRT for nonresectable, nontransplantable and nonablatable HCC patients under a prospective protocol. In Queen Mary Hospital, TACE was the standard of care for nonresectable, nontransplantable and nonablatable HCC patients. In both centers, all HCC patients were evaluated in a multidisciplinary team consisting of hepatobiliary surgeons, oncologists and radiologists. All HCC patients who underwent TACE + SBRT or TACE alone from January 2007 to December 2014 were included. HCC was diagnosed based on typical dynamic imaging criteria, according to American Association for the Study of Liver Diseases (AASLD) guideline [18]. Patients who had major vascular invasion or metastatic disease were excluded.

2.1. TACE + SBRT treatment

All HCC patients unsuitable for curative treatments including liver transplantation, liver resection and radiofrequency ablation were screened for eligibility of TACE + SBRT under a prospective protocol. Criteria for eligibility for curative treatment were the same as in the TACE group. The eligibility of TACE + SBRT were: ≥700 mL of uninvolved liver, an Eastern Cooperative Oncology Group (ECOG) ≤2; Child's score up to B7; an adequate organ function, defined as absolute neutrophil count ≥ 1.5×10^9/L, creatinine ≤ 1.5 of normal, alanine aminotransferase and aspartate aminotransferase (AST) < 2.5 of normal, INR < 1.7 and with no ascites or encephalopathy. Patients with more than five tumor nodules were considered ineligible. There was no limit regarding tumor size.

All patients in TACE + SBRT group would receive one dose of TACE before SBRT. The technique and procedure of TACE were identical to TACE alone group. SBRT was delivered at least 1 week after TACE but the exact interval varied between individual patients. SBRT would commence once the patient's general condition and biochemical parameters were recovered to pretreatment level.

Tumor size and number, uninvolved liver volume and organs at risk (OAR) were assessed by contrast computed tomography (CT). Patients were immobilized with vaclock plus, an in-house body frame with an abdominal compressor for motion management. Four-dimensional CT (4DCT) was acquired by means of a bellows-belt (Philips Medical Systems, Cleveland, USA) placed over the patients' abdomen, which served as a surrogate for 4DCT binning. The 4DCT dataset was sorted into ten respiratory phases, and the phase that corresponded to the mid-ventilation (mean) was chosen as the planning CT (PLCT). Delineation of the gross tumor volume (GTV) was aided by triphasic contrast CT. GTV was defined as HCC focus that demonstrated either as arterial enhancement or washout at portovenous/delayed phase. Clinical target volume (CTV) is defined as GTV with expansion to include lipiodol stained area to cover potential microscopic residual disease. Planning CT was fused with diagnostic triphasic imaging for contouring GTV and CTV. From the liver and tumor motions, the planning target volume (PTV) was generated using the Van Herk margin recipe [17]. Treatment was planned with either a 6 or 10 MV photon based on tumor size and location.

Table 1
Dose constraints of SBRT.

	5–9Gy × 6 fractions group	4Gyx5-10 fractions group
Small bowel/Stomach	5Gy × 6	4Gy × 8
Large bowel	5.5Gy × 6	4Gy × 9
Oesophagus/Gall bladder/Heart	6Gy × 6	4Gy × 10
Rib	8Gy × 6	4Gy × 10
Skin	7Gy × 6	4Gy × 10

Dose and fractionation depended on tumor load and patient liver function. In patients who had tumor size ≤10 cm and ECOG 1–2, 5–8.5Gy for 6 fractions was given. In patients who had tumor > 10 cm and borderline liver function (i.e. Child's B7), the dose per fraction was limited to 4Gy, and more protracted fractionation (6–10 fractions) were used to minimize toxicity. A total dose ranged from 5 to 8.5Gy for 6 fractions to 4Gy for 6–10 fractions were prescribed. The goal was to use the highest allowable dose while respecting normal tissue constraints: normal liver could receive a biologically effective dose with α/β-ratio of 3Gy (BED 3Gy) of $30Gy_3$ < 40% and mean dose < $28Gy_3$ (Table 1). For patients with cirrhosis, a dose constraint of mean liver dose < 28 Gy_3 and $V30Gy_3$ < 40% was required but in patients with normal liver, a mean liver dose < $32Gy_3$ and $V30Gy_3$ < 60% was allowed.

2.2. TACE treatment

Celiac and superior mesenteric arterial and portovenogram were done to define arterial anatomy, tumor size and numbers and to exclude main portal vein occlusion. The right or left hepatic artery would be superselectively catheterized. A mixture of cisplatin (1 mg/ml) with lipiodol in a volume ratio of 1:1 was prepared. A maximum of 60 ml (equivalent to 30 mg cisplatin) mixture was injected under fluoroscopic monitoring. The amount of mixture used would depend on tumor size, number and arterial blood flow. This would be followed by embolization with gelfoam pellets of 1 mm diameter mixed with 40 mg gentamicin. TACE was given twice at 8-week interval.

2.3. Evaluation & determination of treatment response

Contrast CT was done every 3 months in the first 2 years and then every 6 months thereafter. All CT reporting was performed according to the Modified Response Evaluation Criteria for Solid Tumors (mRECIST) criteria [19]. Patients were follow-up regularly. Assessment of performance status, liver & renal function, clotting and alpha-fetoprotein (AFP) were monitored at every clinic visit. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

2.4. Statistics

The study outcomes were OS and progression-free survival (PFS) and both were evaluated from the time of TACE. OS was defined as death from any cause. PFS was defined as the time from treatment until radiological tumor progression or death from any cause. Radiological response was recorded according to the mRECIST. Disease control was defined as complete response (CR), partial response (PR) and stable disease (SD) according to the mRECIST. Owing to the lack of randomization and differences in the 2 groups, propensity score matching was done using the nearest neighboring method in 2:1 ratio (tumor size, number and baseline demographics were used as confounders) to match for characteristic between the TACE and TACE + SBRT group [20,21].

Continuous variables were presented as median and range. Comparison between groups was carried out using Chi-squared or

Table 2
Baseline demographics and tumor characteristics of all patients before and after matching.

	Before propensity score matching			After propensity score matching	
	TACE alone (n = 202)	TACE + SBRT (n = 49)	*p* value	Matched TACE alone (n = 98)	*p* value
Age (years)	69 (20–94)	61 (28–87)	0.011	65 (20–90)	0.861
Gender (n,% male)	160 (79.2)	42 (85.7)	0.303	80 (81.6)	0.535
Hepatitis B carrier (n,%)	131 (64.9)	39 (79.6)	0.048	77 (78.6)	0.490
ECOG*0–2 (n,%)	192 (95.0)	49 (100)	0.237	94 (95.9)	0.376
Child's A (n,%)	164 (81.2)	49 (93.9)	0.031	85 (86.7)	0.190
MELD	8.61 (6–17)	8.47 (6–18)	0.644	8.47 (6–17)	0.672
Bilirubin (umo/L)	14 (3–59)	16 (4–67)	0.865	13 (4–97)	0.434
Albumin (g/L)	37 (21–48)	38 (31–47)	0.009	38 (26–48)	0.071
AST (U/L)	66.5 (17–702)	69 (67–154)	0.397	82 (16–702)	0.613
INR	1.1 (0.8–1.8)	1.1 (0.9–1.2)	0.671	1.1 (0.8–1.5)	0.307
Platelet (x10ˆ9)	161 (25–690)	183 (38–670)	0.333	191 (43–770)	0.301
Creatinine (umol/L)	81 (35–428)	84 (37–165)	1.000	85 (42–428)	0.602
Tumor number (n,%)			0.344		0.152
1	88 (43.6)	27 (55.1)		56 (57.1)	
2	29 (14.4)	7 (14.3)		13 (13.3)	
≥3	85 (42.1)	15 (30.6)		29 (29.6)	
Tumor size (cm)	6.6 (0.5–22.4)	9.5 (4–23.6)	< 0.001	10.1 (1.8–22.4)	0.890
Portal vein invasion (n,%)	0	0	–	0	–
Metastatic disease (n,%)	0	0	–	0	–
AFP⌘ (ng/ml)	61.5 (1–708,100)	49.5 (2–484,100)	0.653	67.5 (1–708,100)	0.724
AFP⌘ ≥ 200 ng/ml (n,%)	77 (38.1)	23 (46.9)	0.258	36 (36.7)	0.234

*ECOG, Eastern Cooperative Oncology Group; AST, aspartate aminotransferase.

Mann-Whitney *U* test where appropriate. Overall and PFS were analyzed using the Kaplan-Meier method and compared with the log-rank test. Variables with $p < 0.1$ in univariate analysis were entered to multivariate analysis using Cox proportional hazard regression model to determine independent predictors to survival. Statistical significance was defined as $p < 0.05$ and all tests were performed two-tailed. All calculations were done using SPSS 22.0.

3. Results

From 2007 to 2014, 49 patients underwent TACE + SBRT and 202 patients had TACE alone. All patients received planned treatment according to the recommendation from a multidisciplinary meeting. All TACE + SBRT patients completed both treatments. Table 2 showed the baseline and pretreatment tumor demographics of all patients. TACE + SBRT group were younger (61 vs. 69 years), had more patients with hepatitis B infection (79.6 vs. 64.9%), Child's A cirrhosis (93.9 vs. 81.2%) and a higher serum albumin (38 vs. 37 g/L). There was no difference in other clinical parameters including gender, ECOG, bilirubin, AST, INR, platelet and creatinine level. Around half of the patients in both groups had a solitary tumor but the median tumor size was larger (9.5 vs. 6.6 cm) in the TACE + SBRT group. Pretreatment AFP and patients with AFP ≥ 200 ng/ml were similar.

3.1. Propensity score matching analysis

Propensity score matching was used to adjust for differences in tumor size, tumor number and baseline demographics between the 2 groups. The matching was done at a ratio of 1:2, 49 patients in TACE + SBRT group were matched to 98 patients who had TACE alone. After propensity score matching, baseline demographics and tumor characteristics were comparable between the 2 groups (Table 2). More than half of the patients in each group had a solitary tumor and less than one-third had ≥3 tumors. The median size of the largest tumor was comparable: 10.1 cm in the matched TACE group and 9.5 cm in the TACE + SBRT group. Pretreatment AFP was similar (67.5 vs. 49.5 ng/ml) and patients who had AFP ≥ 200 ng/ml were also the same (36.7 vs. 46.9%) (Table 2).

3.2. Treatment delivery

In the matched TACE group, cisplatin was the chemotherapy of choice in all patients and the median number of TACE was 2 (range:1–14). In the TACE + SBRT group, 45/49 (91.8%) had one session of TACE before SBRT and the median time from TACE to SBRT was 22 (7–60) days. The median number of TACE at conclusion of the study was 1 (range:1–3). The chemotherapeutic agent was mainly cisplatin 47/49 (96%) and only 2 received doxorubicin. Eighteen patients received 5–8.5Gy for 6 fractions and 31 patients received 4Gy for 5–10 fractions.

3.3. Toxicity after treatment

Both treatments were well tolerated. Risk of severe toxicity was uncommon. TACE + SBRT was associated with more fatigue and hematological abnormality in hemoglobin, platelet and white cell count. TACE patients had more renal and liver impairment and were more likely to have fever. Before treatment, most patients in either group were Child's A (86.7% in the matched TACE group and 93.9% in the TACE + SBRT group, p = 0.190). At 1 month after completion of treatment, in the matched TACE group, 45/98 (46.4%) patients were Child's A and 44/98 (57.1%) were Child's B. In the TACE + SBRT group, 20/49 (40.8%) and 28/49 (57.1%) were Child's A and B respectively at 1 month after treatment and there was no difference between the 2 groups (p = 0.168). None developed classical RILD (Table 3).

3.4. Survival

The median follow-up time for all patients was 13 months. The median survival was better in the TACE + SBRT group (23.9 vs. 10.4 months). The 1-, 2 and 3-year OS were better in the TACE + SBRT group (67.2 vs. 43.9%, 47.1 vs. 24.2% and 36.5 vs. 13.3%, p = 0.003) (Fig. 1a). The 1-, 2- and 3-year PFS were 32.5%, 20.1% and 15.1% in the TACE + SBRT group and 21.4%, 12.1% and 5.1% in the matched TACE group (p = 0.012). The median PFS was longer in TACE + SBRT patients (7.6 vs. 5.7 months) (Fig. 1b). At the time of analysis, there were 32 and 91 deaths in the TACE + SBRT and the matched TACE group respectively. All death in the matched TACE + SBRT (n = 32)

Table 3
Treatment toxicity of all patients after propensity score matching.

Parameters (n,%)	Matched TACE	Matched TACE + SBRT	*p* value
	(n = 98)	(n = 49)	
Fatigue			
0	67 (69.1)	21 (42.9)	< 0.001
1	24 (24.7)	10 (20.4)	
2	6 (6.2)	18 (36.7)	
≥3	0	0	
Fever			
0	78 (80.4)	42 (85.7)	0.008
1	19 (19.6)	4 (8.2)	
2	0	3 (6.1)	
≥3	0	0	
Bilirubin			
0	55 (56.7)	20 (40.8)	0.036
1	19 (19.6)	17 (34.7)	
2	16 (16.5)	6 (12.2)	
≥3	7 (7.2)	6 (12.2)	
Albumin			
0	10 (10.3)	33 (67.3)	< 0.001
1	53 (54.6)	7 (14.3)	
2	34 (35.1)	9 (18.4)	
≥3	0	0	
AST			
0	10 (10.3)	25 (51)	< 0.001
1	41 (42.3)	10 (20.4)	
2	32 (33)	5 (10.2)	
≥3	14 (14.4)	9 (18.4)	
INR			
0	62 (63.9)	48 (98)	< 0.001
1	32 (33)	1 (2)	
2	2 (2.1)	0	
≥3	1 (1)	0	
Platelet			
0	59 (60.8)	20 (40.8)	0.021
1	31 (32)	17 (34.7)	
2	4 (4.1)	8 (16.3)	
≥3	3 (3.1)	4 (8.2)	
White cell			
0	88 (90.7)	33 (67.3)	0.001
1	8 (8.2)	8 (16.3)	
2	1 (1)	7 (14.3)	
≥3	0 (0)	1 (2)	
Hemoglobin			
0	97 (100)	30 (61.2)	< 0.001
1	0	10 (20.4)	
2	0	6 (12.2)	
≥3	0	3 (6.1)	
Creatinine			
0	69 (71.1)	44 (89.8)	0.017
1	20 (20.6)	5 (10.2)	
2	5 (5.2)	0	
≥3	3 (3.1)	0	

and 78/91 (85.7%) deaths in the matched TACE group were cancer-related. In the matched TACE group, 5 patients died of gastrointestinal bleeding, 3 died of cardiovascular event, 4 died of sepsis and 1 died after road traffic accident.

Fig. 2a and b showed the best mRECIST and AFP trends of the 2 groups. In the matched TACE group, radiological CR and PR only occurred in 5 (5.2%) patients respectively, and around half of the patients (45/97, 46.4%) had SD. The rest (42/97, 43.3%) never had radiological disease control. In contrast to the TACE + SBRT group, only 1 (2%) patient never had disease control after TACE + SBRT. This patient developed a new HCC focus in liver but the SBRT-treated lesion had PR. Around 1/5 of the patients had radiological CR (9/49, 18.4%) and the majority of the patients had PR (36/49, 73.5%).

3.5. Predictors for overall and progression-free survival

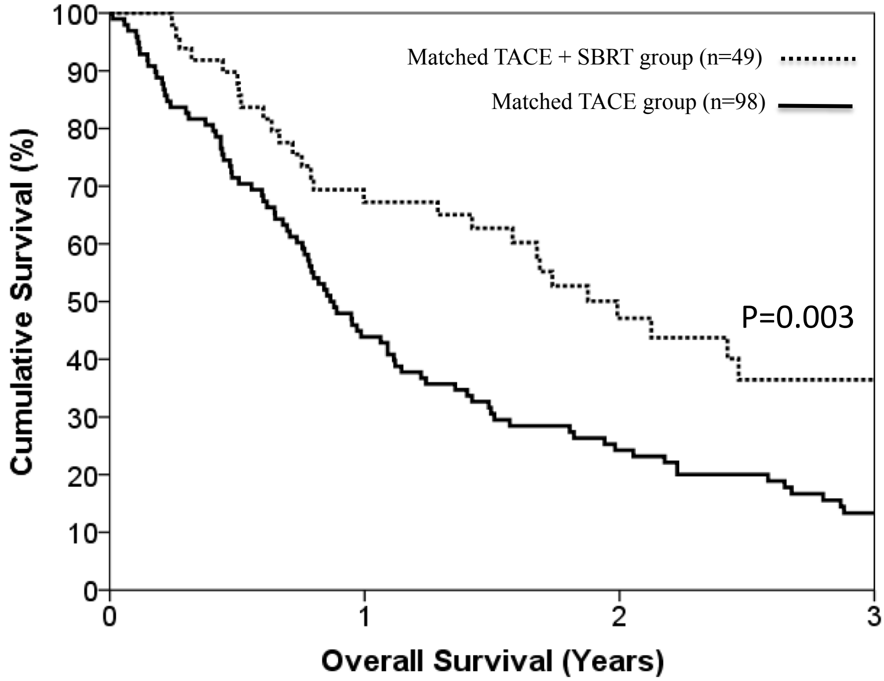
In multivariable analysis, pretreatment AFP ≥ 200 ng/ml [HR = 2.37 (1.60–3.49), p < 0.001], large tumor size [HR = 1.07 (1.02–1.12), p = 0.003] and multiple tumors [HR = 1.10 (1.03–1.16), p = 0.003] were associated with poorer OS. TACE + SBRT as treatment arm was associated with significantly better OS [HR = 0.37 (0.24–0.56), p < 0.001] (Table 4). Similar predictors were found for PFS; pretreatment AFP ≥ 200 ng/ml [HR = 2.31 (1.60–3.33), p < 0.001] and tumor size [HR = 1.09 (1.05–1.13), p < 0.001] were predictors for inferior PFS while TACE + SBRT had significantly better PFS [HR = 0.47 (0.32–0.70), p < 0.001]. (Table 4).

4. Discussion

In our study, we have demonstrated a substantial survival benefit after TACE + SBRT than TACE alone for large HCC with median tumor size of 10 cm. After propensity score matching, OS after TACE + SBRT was more than doubled than TACE alone (23.9 vs. 10.4 months). The 1- and 3-year PFS was also better in the TACE + SBRT patients (32.5 vs. 21.4% and 15.1 vs. 5.1%). TACE + SBRT was well tolerated and no patient developed RILD. SBRT was the main contributing factor for prolonging overall and PFS as most patients in the TACE + SBRT group received only one session of TACE.

There were a few prospective series about SBRT for nonresectable HCC and showed a 2-year OS at 34–68.7% and PFS at 33.8–48% [10–16]. At first glance, our 1- and 3-year OS of 67.2% and 36.5% and 1- and 3-year PFS of 32.5% and 15.1% might appear inferior. However, in most of these studies, the median tumor size was around 5 cm for SBRT patients [12,14–16,22]. In contrast, the present study included HCC with median tumor size over 10 cm for TACE + SBRT approach. Our data suggested that by combining TACE + SBRT, it improved survival and local control rate for large nonresectable HCC. Although TACE is widely accepted as the standard of care for nonresectable HCC patients in different clinical guidelines [23–26] and it is the only treatment that demonstrated consistent survival benefits [4,27], TACE is ineffective for large HCC and the 2-year survival was only 42% and 0% for tumor size of 5–7 cm and ≥ 8 cm respectively [28]. Despite the poor outcomes, TACE remains the treatment of choice for large nonresectable HCC patients in most centers as these patients are the least likely to have transplant, resection or radiofrequency ablation. The addition of SBRT to TACE has led to a significant increase in OS among large nonresectable HCC patients, around half survived for 2 years after TACE + SBRT. This was in great contrast to patients who had TACE alone; the median survival was 10.4 months only. Disease control was superior (98 vs. 56.7%) in the TACE + SBRT group. It also explained the delay in tumor progression and death in the TACE + SBRT group. More than 40% of patients in the TACE group never had disease control (i.e. tumor progression) and they had a worse prognosis. Inevitably, most tumors progressed and the majority of deaths (110/123, 89.4%) were cancer-related. It was because our cohort included mainly Child's A patients with advanced tumor stage, therefore the cause of death was mainly from cancer but not decompensated cirrhosis. As the tumor size was larger in the TACE + SBRT group and baseline demographics were also different, propensity score matching was performed in order to control for differences in tumor size and numbers, which were the main determinants of outcomes after TACE or SBRT. Treatment with TACE + SBRT predicted superior OS and PFS in multivariate analyses reaffirmed our hypothesis that TACE + SBRT offered better local control and eventually led to better survival.

Our SBRT protocol adopted a radiation dose fractionation according to the constraints of OAR. Fractionated RT of 4Gy in 5–10 fractions was prescribed to patients with tumor size > 10 cm to improve tolerability. Large tumors were more often in close proximity to the OARs and had less liver reserve; trade-offs of dose were more frequently required to mitigate radiation-induced side effects, but in turn, it might compromise local control. A study showed that fractionated RT offers a dosimetric advantage over 5-fractions regime in large HCCs close to OARs [29]. The high disease control rate in the present study showed that



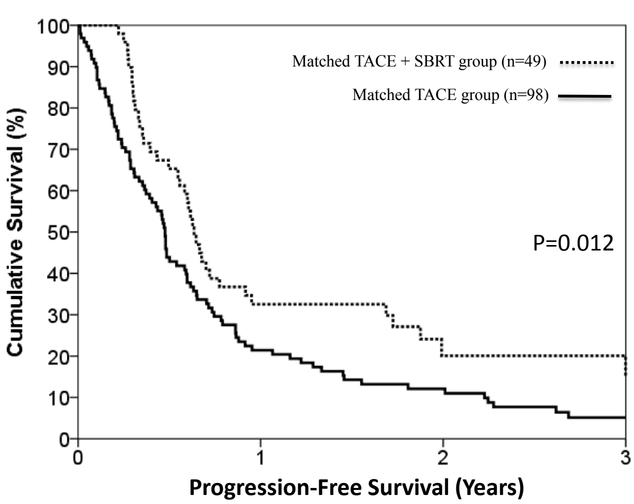
Number at risk:

Matched TACE + SBRT group	49	31	16	8
Matched TACE group	98	43	23	11

Fig. 1. a and b. Overall and progression-free survival of matched TACE and matched TACE + SBRT patients.

SBRT was feasible for large HCC.

Combining TACE with SBRT was well tolerated. No patient developed classical RILD. The risk of toxicity ≥ grade 3 was low, and most were related to transient, reversible liver function derangement. An important thing to note is the interval between TACE and SBRT was 22days and the interval was < 6 weeks in over 90% of the patients. Many patients in our cohort had concomitant cirrhosis and there was always a concern whether combining TACE + SBRT would cause more toxicity. In the present study, we have demonstrated an interval of 3 weeks should be adequate for liver function to recover and the addition



Number at risk:

Matched TACE + SBRT group	49	14	5	3
Matched TACE group	98	21	11	4

Fig. 1. (*continued*)

of SBRT to TACE did not lead to unacceptable toxicities. Careful selection of candidates for SBRT was crucial. At least 700 ml of uninvolved liver (whole liver volume minus GTV) was required in order to be eligible for SBRT [30]. The same eligibility requirement was adopted in the on-going RTOG 1112 trial. Mean liver dose was an independent factor that associated with Child score progression after radiotherapy and a mean liver dose > 28Gy was associated with a 5% risk of RILD [31,32]. The risk of liver function deterioration after TACE and radiotherapy was more common if V30 > 40% for large HCC [33]. Therefore our institutional protocol opted for a minimum requirement of ≥700 ml uninvolved liver with the mean liver dose < $28Gy_3$ and $V30Gy_3$ < 40% as dose constraints of liver to guide radiotherapy dose prescription.

Our findings have to be confirmed by a large-scale randomized trial. Before we incorporate SBRT in the treatment algorithm for non-resectable HCC patients, there are questions remain unanswered. The most important question is appropriate patient selection. The optimal tumor number and size for SBRT has yet to be defined. There is always a dilemma of trying to benefit more patients while maintaining a satisfactory post-SBRT outcome. In the present study, we have demonstrated SBRT to large HCC as large as 10 cm was effective and safe. Cumulative radiation dosage increases with tumor size and the tolerance of OARs limits the maximum dose of radiation that can be safely delivered. Most studies accepted Child's A/B7 patients for SBRT and suggested that SBRT is safe for these patients [10–13,22]. However, Child's classification is subjective. A more objective measurement such as indocyanine green and transient elastography, that is used extensively in liver surgery and hepatology to evaluate liver function and degree of fibrosis/cirrhosis should be explored as part of the evaluation process for SBRT [34,35]. Immunotherapy will soon become the new standard of care for metastatic and advanced HCC [36]. Currently, antibodies against programmed cell death protein 1 (PD-1) or its ligand.

(PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)

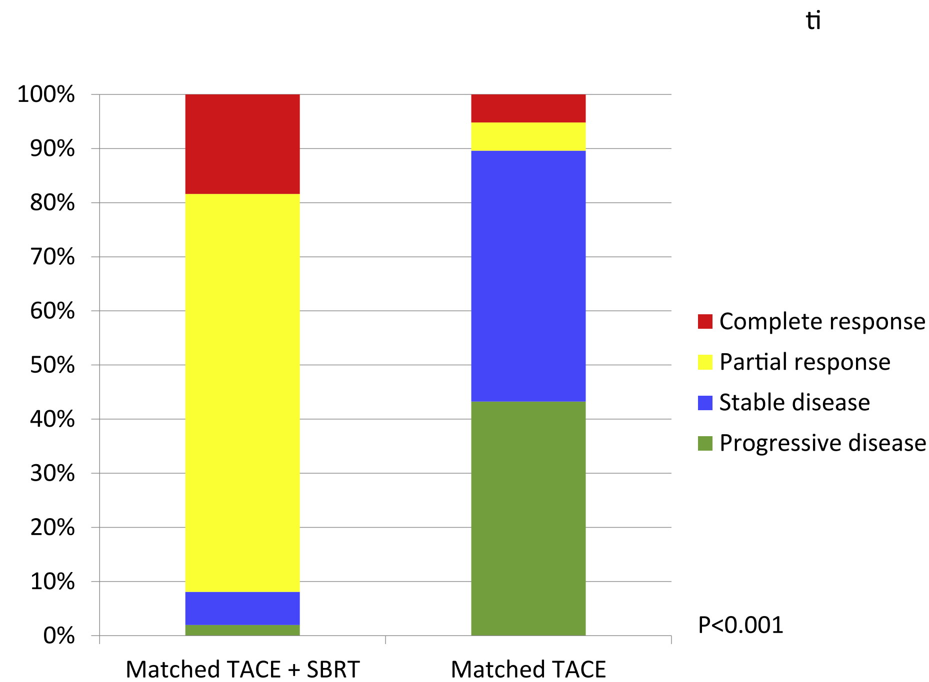


Fig. 2. The best mRECIST of matched TACE and matched TACE + SBRT patients.
b. The trend of AFP before and after treatment for matched TACE and matched TACE + SBRT patients.

are under investigation for treating HCC [37–39]. It was postulated that radiotherapy might have synergistic effects with immunotherapy. Radiotherapy exerts a direct cytotoxic effect to tumor cells, it also alters the tumor microenvironment and enhances anti-tumor immunity [40]. In a phase 1 study, SBRT was used in combination with *anti*-PD1 antibody for advanced solid tumors and showed promising early results

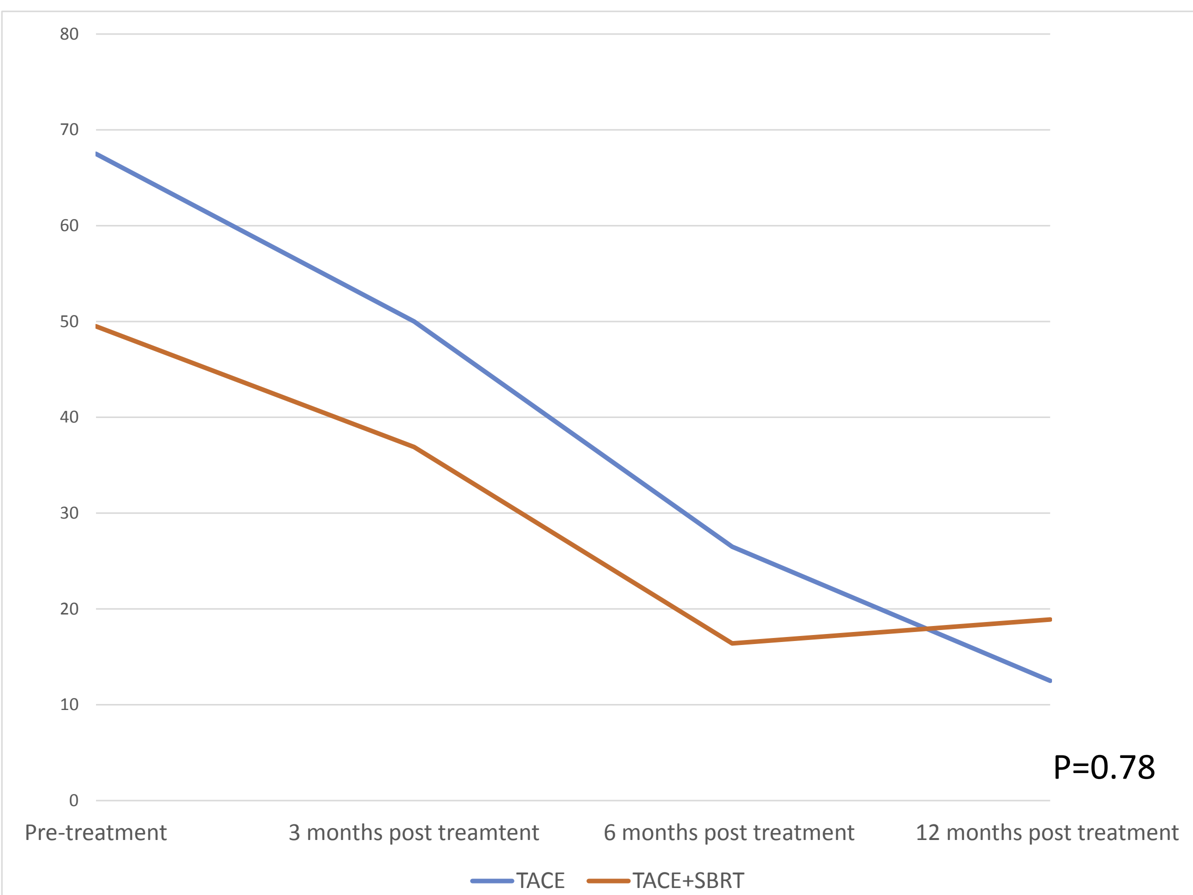


Fig. 2. (*continued*)

Table 4
Univariate and multivariate analyses of potential prognostic factors affecting overall and progression-free survival.

	Overall survival				Progression-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Gender (male)	0.89 (0.56–1.43)	0.636			0.72 (0.45–1.16)	0.177		
Age	0.99 (0.97–1.00)	0.123			0.99 (0.98–1.01)	0.315		
Hepatitis B infection	1.16 (0.81–1.66)	0.431			1.27 (0.90–1.80)	0.179		
Hepatitis C infection	1.18 (0.86–1.62)	0.300			1.14 (0.84–1.55)	0.398		
AFP ≥ 200 ng/ml	2.22 (1.53–3.20)	< 0.001	2.37 (1.60–3.49)	< 0.001	2.17 (1.52–3.90)	< 0.001	2.31 (1.60–3.33)	< 0.001
Tumor size	1.09 (1.05–1.13)	< 0.001	1.07 (1.02–1.12)	0.003	1.09 (1.05–1.13)	< 0.001	1.09 (1.05–1.13)	< 0.001
Tumor number	1.11 (1.06–1.17)	< 0.001	1.10 (1.03–1.16)	0.003	1.08 (1.03–1.14)	0.002		
Platelet	1.00 (1.001–1.003)	0.001			1.002 (1.001–1.003)	0.001		
Albumin	0.99 (0.96–1.02)	0.461			0.100 (0.97–1.02)	0.689		
Bilirubin	0.10 (0.98–1.01)	0.778			1.00 (0.98–1.02)	0.979		
INR	1.07 (0.44–2.63)	0.880			0.88 (0.36–2.16)	0.876		
Creatinine	1.00 (0.10–1.01)	0.769			0.997 (0.991–1.003)	0.375		
Child's C	1.25 (0.72–2.19)	0.430			1.00 (0.57–1.74)	0.996		
ECOG	1.92 (0.70–5.26)	0.205			1.33 (0.49–3.61)	0.578		
TACE + SBRT as treatment arm	0.55 (0.37–0.82)	< 0.001	0.37 (0.24–0.56)	< 0.001	0.62 (0.42–0.90)	0.013	0.47 (0.32–0.70)	< 0.001

HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein; ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization; SBRT, stereotactic body radiation therapy.

[41]. Combining SBRT with immunotherapy will be of great interests for the treatment of advanced HCC [42].

Our study does have some limitations. It was a retrospective study with a small patient number. A randomized controlled trial would be ideal to resolve the controversy and to determine the true benefits of SBRT in nonresectable HCC patients. Nonetheless, propensity score matching was used to minimize the effects of possible confounding factors and selection bias. Our data were obtained through collaboration between 2 institutions that evaluated primary HCC within the same study period. Despite sharing the same management protocol for HCC, there might still be selection and management biases between patients who underwent TACE and TACE + SBRT.

There is an unmet need to improve the outcome of intermediate/locally advanced HCC [43]. In the present study, TACE + SBRT resulted in a 63% and 53% reduction in OS and PFS hazard ratio. Our study provided strong preliminary evidence that by combining TACE and SBRT, there were survival benefits for nonresectable HCC patients. Data from a randomized trial is needed, to better define patients' selection and to demonstrate disease control and survival benefits of TACE + SBRT.

5. Conclusion

With propensity score matching, the 1- and 3-year OS were better in the TACE + SBRT group (67.2 vs. 43.9% and 36.5 vs. 13.3%). The 1- and 3- year PFS was also better in the TACE + SBRT patients (32.5 vs. 21.4% and 15.1 vs. 5.1%). TACE + SBRT was well tolerated with none developed RILD. TACE + SBRT was superior to TACE in nonresectable HCC.

Conflicts of interest

Nil.

Acronyms used:

AASLD American Association for the Study of Liver Diseases
AFP alpha-fetoprotein
CR complete response
CT computed tomography
ECOG Eastern Cooperative Oncology Group
HCC hepatocellular carcinoma
mRECIST Modified Response Evaluation Criteria for Solid Tumors
PD progressive disease
PR partial response
RILD radiation-induced liver disease
SBRT stereotactic body radiation therapy
SD stable disease
TACE transarterial chemoembolization

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