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ORIGINAL ARTICLE

Combined stereotactic body radiotherapy and trans-arterial chemoembolization as initial treatment in BCLC stage B–C hepatocellular carcinoma

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Abstract

Purpose We retrospectively evaluated the efficacy and safety of stereotactic body radiotherapy (SBRT) combined with trans-arterial chemoembolization (TACE) as initial therapy in Barcelona Clinic Liver Cancer (BCLC) system stage B–C hepatocellular carcinoma (HCC).

Patients and methods Seventy-two patients received a single dose of TACE followed by SBRT 4 weeks later. All patients had tumor sizes ≥5 cm, at least 700 ml of disease-free liver, Child–Pugh (CP) score ≤ B7 and tumor nodules ≤5. SBRT dose, ranging from 6 × 5–8 Gy or 5–10 × 4 Gy, was individualized according to normal tissue constraints. No subsequent scheduled treatment was delivered unless disease progression was observed. Local control (LC), overall survival (OS), progression-free survival (PFS), response rate (RR), and toxicity were evaluated.

Results The patients' characteristics were: median age 60 years (range 28–87 years); CP score A/B (n = 68/4); BCLC stage B/C (n = 51/21); solitary/multifocal (n = 37/35); portal vein invasion (n = 18). The median tumor size and GTV were 11.2 cm (range 5.0–23.6 cm) and 751 cm^3 (range 41–4009 cm^3), respectively. The median equivalent dose in 2 Gy per fraction (EQD2, $\alpha/\beta = 10$) was 37.3 Gy2 (range, 28–72 Gy2). The median follow-up time was 16.8 months (range, 3–96 months). The objective RR was 68% and the 1-year LC rate was 93.6% (95% CI, 87.6–100%). The median OS was 19.8 months (95% CI, 11.6–30.6 months). SBRT-related grade 3 or higher adverse gastrointestinal events and treatment-related death occurred in three (2.8%) and one patient (1.4%) respectively. No patient developed classical radiation-induced liver injury.

Conclusion Our experience suggests that combined TACE and SBRT can be a safe and effective initial therapy for BCLC stage B–C HCC with appropriate patient selection. Further prospective trials are warranted.

Keywords Stereotactic body radiotherapy · Transarterial chemoembolization · Initial therapy · BCLC stage B-C · Hepatocellular carcinoma

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Kombinierte stereotaktische Körperstamm-Strahlentherapie und transarterielle Chemoembolisation als Erstlinientherapie beim hepatozellulären Karzinom im BCLC-Stadium B–C

Zusammenfassung

Zielsetzung Wir bewerteten retrospektiv Wirksamkeit und Sicherheit der stereotaktischen Körperstamm-Strahlentherapie (SBRT) in Kombination mit transarterieller Chemoembolisation (TACE) als Erstlinientherapie für Leberzellkarzinome (HCC) im Stadium B–C nach dem Barcelona-Klinik-Leberkrebs(BCLC)-System.

Patienten und Methoden Es bekamen 72 Patienten eine einzige TACE-Anwendung gefolgt von einer SBRT 4 Wochen später. Alle Patienten hatten ≥5 cm, mindestens 700 ml tumorfreie Leber, einen Child-Pugh-Score (CP) ≤ B7 und Läsionen ≤ 5. Die SBRT-Dosen im Bereich von 6 × 5–8 Gy oder 5–10 × 4 Gy wurden bezüglich notwendiger Einschränkungen im Normalgewebe individualisiert. Eine weitere Behandlung wurde nur bei entsprechender Progression der Erkrankung durchgeführt. Der primäre Endpunkt war die lokale Kontrolle (LK). Sekundäre Endpunkte umfassten Gesamtüberleben (GS), progressionsfreies Überleben (PFÜ), Ansprechrate (AR) und Toxizität.

Ergebnisse Patientenmerkmale waren: mittleres Alter 60 Jahre (Spanne 28–87 Jahre); CP-Score A/B (n = 68/4); BCLC-Stadium B/C (n = 51/21); solitär/multifokal (n = 37/35); Pfortaderinvasion (n = 18). Mittlere Tumorgröße und GTV betrugen 11,2 cm (Spanne 5,0–23,6 cm) bzw. 751 cm^3 (Spanne 41–4009 cm^3). Die mittlere Äquivalentdosis in 2 Gy pro Fraktion (EQD2, $\alpha/\beta = 10$) betrug 37,3 Gy2 (Spanne 28–72 Gy2). Die mittlere Nachbeobachtungszeit war 16,8 Monate (Spanne 3–96 Monate). Die Ziel-AR betrug 68 % und die 1-Jahres-LK 93,6 % (95 %-Konfidenzintervall [KI] 87,6–100 %). Das mediane GS lag bei 19,8 Monaten (95 %-KI 11,6–30,6 Monate). SBRT-induzierte Nebenwirkungen vom Grad 3 oder höher traten bei 3 Patienten (2,8 %) bzw. behandlungsbedingte Todesfälle bei 1 Patienten (1,4 %) auf. Kein Patient entwickelte eine klassische strahleninduzierte Leberschädigung.

Schlussfolgerungen Unsere Erfahrung zeigt, dass bei entsprechender Patientenauswahl die Kombination von TACE und SBRT eine sichere und effektive Erstlinientherapie für das HCC im BCLC-Stadium B–C sein kann. Prospektive Studien sind gerechtfertigt.

Schlüsselwörter Stereotaktische Körperstamm-Strahlentherapie · Transarterielle Chemoembolisation · Erstlinientherapie · BCLC-Stadium B–C · Hepatozelluläres Karzinom

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and ranks as the second cancer-related cause of death globally, with most of the disease burden in Asia and Africa [1]. One of the most widely adopted staging systems for HCC is the Barcelona Clinic Liver Cancer (BCLC) system, which was developed mainly based on hepatitis C virus (HCV)-related HCC [2]. This system has the advantage of linking the disease staging to treatment recommendations and therefore its therapeutic flowchart plays a pivotal role in patient management and designing clinical trials in Western countries [3].

However, in Asian countries, a majority of HCC is associated with the endemic hepatitis B virus (HBV) infection [4], as opposed to their Western counterparts where HCV infection and alcoholic cirrhosis are two major attributing factors [5]. The natural history and prognosis of HBV- and HCV-related HCC are different [6]; patients with HBV-related HCC often show sizable tumors [7]. It is therefore recognized that the therapeutic recommendation of the BCLC system might not be applicable in Asian countries [8]. For example, among patients with intermediate-stage HCC, trans-arterial chemoembolization (TACE) is the recommended upfront therapy [9, 10]. However, its treatment effect seems to be poor in large tumors, with reported 2-year survival of HCC patients receiving TACE of 42% versus 0% for tumor sizes of 5–7 cm and ≥8 cm, respectively [11]. The outcome is even worse in advanced stage HCC, for which sorafenib is the standard therapy. Sorafenib rarely induces tumor shrinkage, with response rate of 2–3%, and the survival benefit seems to be limited [12, 13].

All these factors highlight the unmet need of optimizing the loco-regional therapy effect in the management of HBV-related HCC. For example, more aggressive surgical approaches that are widely adopted in Asian countries were associated with better clinical outcome [14], but many advanced stage patients are surgically or medically inoperable. For non-surgical candidates, stereotactic body radiotherapy (SBRT) has emerged as a promising local therapy associated with impressive local control [15–17]. At our institution, SBRT was initially utilized in patients who failed or were intolerant to TACE with promising results, which, in turn, prompted us to combine TACE and SBRT as standard upfront loco-regional therapy in those patients who are not amendable to curative surgery.

To date, in patients with HBV-related large HCC, there are a limited number of reports to evaluate the combination

of TACE and SBRT as initial therapy. We therefore retrospectively analyze our clinical outcome of combined SBRT and TACE in BCLC stage B or C HCC.

Patients and methods

Patients

The diagnosis of HCC was established either by biopsy or by the American Association for the Study of Liver Diseases (AASLD) criteria with characteristic enhancement on two imaging modalities in the presence of cirrhosis. From 2008 to 2015, 72 consecutive BCLC B–C patients who were treated with combined TACE and SBRT according to our institutional protocol were included in this IRB-approved retrospective analysis. Patients were offered treatment under the combined TACE/SBRT protocol if they were unsuitable for resection, liver transplantation, or local ablation therapies, and had a minimum of 700 mL of uninvolved liver, an Eastern Cooperative Oncology Group (ECOG) performance score ≤2, a Child–Pugh (CP) liver score of A to B7, an adequate organ function defined as absolute neutrophil counts (ANC) ≥1.5 × 109/l, creatinine ≥1.5 × ULN, alanine transaminase (ALT) or aspartate transaminase (AST) <2.5 × upper limit of normal (ULN), international normalised ratio (INR) <1.7, and no ascites or encephalopathy clinically. Extra-hepatic diseases were allowed, provided the greatest burden of disease was hepatic. Patients with main portal vein thrombosis (PVT), diffusely infiltrative disease, or more than five tumor nodules were not offered the combined therapy. There was no limit regarding tumor size.

Treatment

TACE was performed by supra-selective cannulation of the supplying tumor artery. The emulsion was prepared by mixing lipiodol with cisplatin in a 1:1 ratio. Various amounts of the emulsion were injected slowly under fluoroscopic monitoring according to the size of the tumor and the arterial blood flow. The maximum dosage of cisplatin and lipiodol injected was 40 mg and 20 ml for each treatment session, respectively. The interval between TACE and simulation computed tomography (CT) was one week, and that between TACE and the start of SBRT was four weeks. The first patients ($n = 18$) from 2008–2010 were treated using respiratory gating and the subsequent patients ($n = 55$) from 2011–2015 were treated by a four-dimensional cone beam computed tomography (4DCBCT) guided-approach. The gross tumor volume (GTV) was defined on the plain non-contrast CT when the lipiodol enhancing tumor was visualized. Otherwise, it was defined on the contrast CT, which was usually best visualized at the arterial phase (as hyperintensity) or at the delayed portovenous phase, and included the lipiodol-stained area.

For the first cohort of patients treated with gating, treatment planning was based on 4DCT simulation. The clinical target volume (CTV) was defined as GTV plus a margin of 0 to 5 mm. The internal target volume (ITV) was defined as the composite CTV from the 40 to 60% of respiratory phases. The planning target volume (PTV) margin from ITV ranged from 3 to 5 mm. Radiation was delivered mostly by coplanar 1–2 dynamic conformal arcs, or in a few cases, 5–7 static conformal fields on a 6 MV linac. The treatment setup was performed with the ExacTrac stereotactic body setup system (BrainLab Ltd, Feldkirchen, Germany) together with a stereotactic frame and pre-treatment CT verifications, as described in Wong et al. [18]. For treatments of more than one lesion, multiple isocenters were applied to individual lesions.

For the second cohort of patients treated with the 4DCBCT-guided approach, treatment planning was primarily based on the mid-ventilation concept [19] Volumetric modulated arc radiotherapy (VMAT) was planned on a dual-energy 6 MV and 10 MV linac for all patients, with lesions grouped into a single or dual isocenter for multiple lesions. Technical details of the extraction of the mid-ventilation CT images from the 4DCT and subsequently the formulation of the mid-ventilation PTV at our institution were described in [20]. Pre-treatment 4DCBCT was acquired per treatment isocenter for every fraction. The tumor localization was based on the lipiodol retention whenever it was visible or the diaphragm as a tumor surrogate [21].

The prescribed SBRT dose, ranging from 5.0–6.5 Gy × 6 fractions or 4.0 Gy × 6–10 fractions, was individualized according to the normal tissue constraints. Dose constraints included the normal liver receiving a biological effective dose with α/β ratio of 3 Gy (BED_{3Gy}) of 30 Gy_3 < 40% and mean dose <28 Gy_3. Doses to 0.1 cc of duodenum, stomach, and small bowel were limited to 4 Gy per fraction for 8 fractions or to 5 Gy per fraction for 6 fractions. We allowed minor dose constraint violations in patients without HBV and HCV carrier and no evidence of cirrhosis.

Evaluation

Patients were assessed every 3 months for the first 2 years and then every 4 months thereafter for treatment response and resectability of lesions. Physical examination and blood work were performed at every follow-up. A tri-phasic liver CT was obtained at 3 months after SBRT and then every 3 months in the first year and every 6 months thereafter. At our institution, the tumor response was routinely measured using Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1.

Local control (LC), progression-free survival (PFS), overall survival (OS), alpha-fetoprotein (AFP) response, and toxicity were evaluated. LC was defined as the absence of progressive disease within the PTV. Patients with liver resection or transplant during follow-up were censored for LC. A new lesion developing outside the PTV was regarded as intra-hepatic out-of-field failure. PFS was defined as the period from the date of starting TACE to the time of disease progression or the time at which the patient passed away, whichever occurred first. OS was calculated from the start of TACE until the date of final follow-up or death. An AFP response was defined as a drop of at least 20% from baseline.

Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Toxicities were defined as adverse events that occurred >3 months after SBRT. All newly developed toxicities or toxicities that had progressed to 1 grade higher compared to baseline before treatment were considered as adverse events from SBRT. A grade 5 hepatic failure caused by SBRT was defined as death from hepatic failure after the development of acute grade 3 liver toxicities in the first 6 months without intra-hepatic progression.

Statistics

Wilcoxon signed-rank test was used to compare the AFP level at different time points. LC, PFS, and OS were calculated by Kaplan–Meier curves. The log-rank test was used to compare outcomes among survival curves for prognostic factors. Any factors that were significant in univariable analyses were subjected to multivariable analyses using the Cox proportional hazards regression model. A statistical level of $p < 0.05$ was considered significant. R version 3.2.5 (Vienna, Austria) was used for statistical analysis.

Results

Patients and treatment

From 2008 to 2015, 72 patients were treated under the combined TACE/SBRT protocol as presented above. Baseline patient and treatment characteristics are presented in Table 1. 51 patients (61%) had BCLC stage B disease, while remaining 21 patients (39%) had BCLC stage C disease. Among the patients with BCLC stage C disease, 13 (62%) had branch portal vein (PV)/inferior vena cava (IVC) invasion or minor thrombosis, 2 (10%) had a lymph node metastasis, 1 (5%) had distant metastases, 3 (14%) had both PV invasion and lymph node involvement, and 2 (9%) had both PV invasion and distant metastases. The median tumor size was 11.5 cm (range: 5.0–23.6 cm). 59 patients (82%) are

Table 1 Patient and Treatment Characteristics

	Number of patients (%)
Age (years)	
Median	60
Range	28–87
Sex	
Male	61 (85%)
Female	11 (15%)
Child–Pugh score	
A5	55 (76%)
A6	13 (18%)
A7	4 (6%)
Etiology[a]	
Hepatitis B	61 (84.7%)
Hepatitis C	7 (9.7%)
Alcohol	3 (4.2%)
Unknown	1 (1.4%)
ECOG	
0	51 (71%)
1	4 (6%)
2	17 (22%)
BCLC stage	
B	51 (71%)
C	21 (28%)
TNM stage	
I	19 (26%)
II	0 (0%)
III	45 (63%)
IV	8 (11%)
Tumor vascular thrombosis	
No	54 (75%)
Yes	18 (25%)
Extra-hepatic metastasis	
No	64 (89%)
Yes	8 (11%)
Number of lesions	
Solitary	37 (51%)
Multi-nodular	35 (49%) 2 lesions = 18[a] 3–5 lesion = 17[b]
Baseline AFP	
Median	893.5
Range	1.5–>800,000
Size of largest lesion, cm	
Median	11.2
Range	5–23.6
GTV size, cc	
Median	751.5
Range	41–4009
PTV size, cc	
Median	1065
Range	180.6–4468

Table 1 (Continued)

	Number of patients (%)
Prescription dose, Gy (EQD2, α/β = 10)	
Median	37.3
Range	28–72
Liver mean dose, Gy (EQD2, α/β = 3)	
Median	24.35
Range	14–36.1
V30, Gy (EQD2, α/β = 3)	
Median	35.3
Range	11–44

[a]SBRT treated all lesions in all 18 patients
[b]SBRT treated all lesions in 11 patients, and in the dominant tumor and its contagious lesions in the remaining 6 patients
ECOG Eastern Cooperative Oncology Group, *BCLC* Barcelona Clinic Liver Cancer, *AFP* Alpha-feto Protein, *GTV* Gross Tumor Volume, *PTV* Planning Target Volume, *EQD2* Equivalent dose in 2 Gy per fraction, *V30* Liver volume percentage received more than 30 Gy

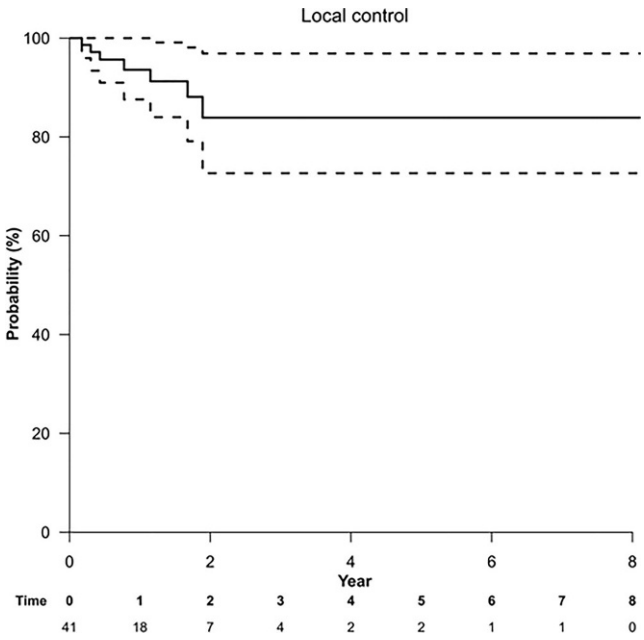

Fig. 1 Local control of patients. Unit of time: Year. *Solid line* represented the KM curve and *dasehd line* represented its confidence interval

hepatitis B carriers. No patients had received previous treatment. No patient dropped out after TACE, and all except one patient (98.6%) completed the planned SBRT treatment. The median prescription dose in an equivalent dose of 2 Gy per fraction (EQD2, $\alpha/\beta = 10$) was 37.3 Gy_{10} (range, 23.8–72.0 Gy_{10}). The median interval between TACE and SBRT was 22 days (range, 10–66 days).

Response and local control

The median follow-up was 16.8 months (range, 3–96 months). At 1 year and 2 years, there were 41 and 19 patients available for the analysis of local control, respectively. The corresponding LC at 1 year and 2 years was 93.6% (95% confidence interval CI = 87.6–100%) and 83.9% (95% CI = 72.7–96.9%), respectively (Fig. 1). Among the 66 patients who had at least one CT assessment, the best response after full treatment was a partial response (Supplementary material Fig. S1) occurring in 45 patients (68%) and otherwise a stable disease was found in 21 patients (32%). The median time to local recurrence was not reached. The size of the lesion was the only significant factor associated with local control (<15 cm vs. ≥15 cm, hazard ratio HR = 3.18, 95% CI = 1.74–5.81).

Among those patients with AFP elevation, an AFP response was observed in 82.6% of the patients. The median AFP was significantly different from baseline at 3 months, 6 months, 9 months, and 12 months after full treatment (Fig. 2).

Overall survival and time to progression

At the time of analysis, 3 patients (4.2%) were lost during follow-up while 43 patients (59.7%) had died. Death was related to cancer in 39 patients (90.7%) while 1 patient (2.3%) died of treatment-related liver failure, 2 patients (4.7%) died due to post-operative complications in subsequent treatments, and the remaining patient (2.3%) died because of unrelated causes. The median OS of the entire cohort was 19.9 months (95% CI, 11.6–30.6 months). For BCLC stage B and C, the median OS was 25.7 months (95% CI, 16.9–38.7 months) and 8.9 months (95% CI, 5.9–33.1 months), respectively (Fig. 3), with statistical significance show ($p = 0.09$). Among the patients with BCLC stage C disease ($n = 21$), the median OS of patients without extra-hepatic disease ($n = 13$) was significantly better than among those with extra-hepatic metastases ($n = 8$; 11.5 months versus 6.0 months, $p < 0.04$). Significant factors associated with OS for the whole patient group were the lesion size, the presence of extra-hepatic disease, and whether the patient received post-TACE/SBRT therapies (surgery, sorafenib, repeated TACE) or not (Table 2).

The median time to progression was 7.2 months (95% CI, 5.3–10.1 months). The PFS was 9.1 months (95% CI, 7.2–19.8 months) and 4 months (95% CI, 3.6–6.3 months) for BCLC B and C patients, respectively. For the first site of progression after initial treatment, 32 patients (56.1%) had new isolated out-of-field lesions in the liver, 10 (17.5%) had distant metastases, 3 (5.3%) had isolated in-field recurrences, while 12 (21.1%) had progression in multiple

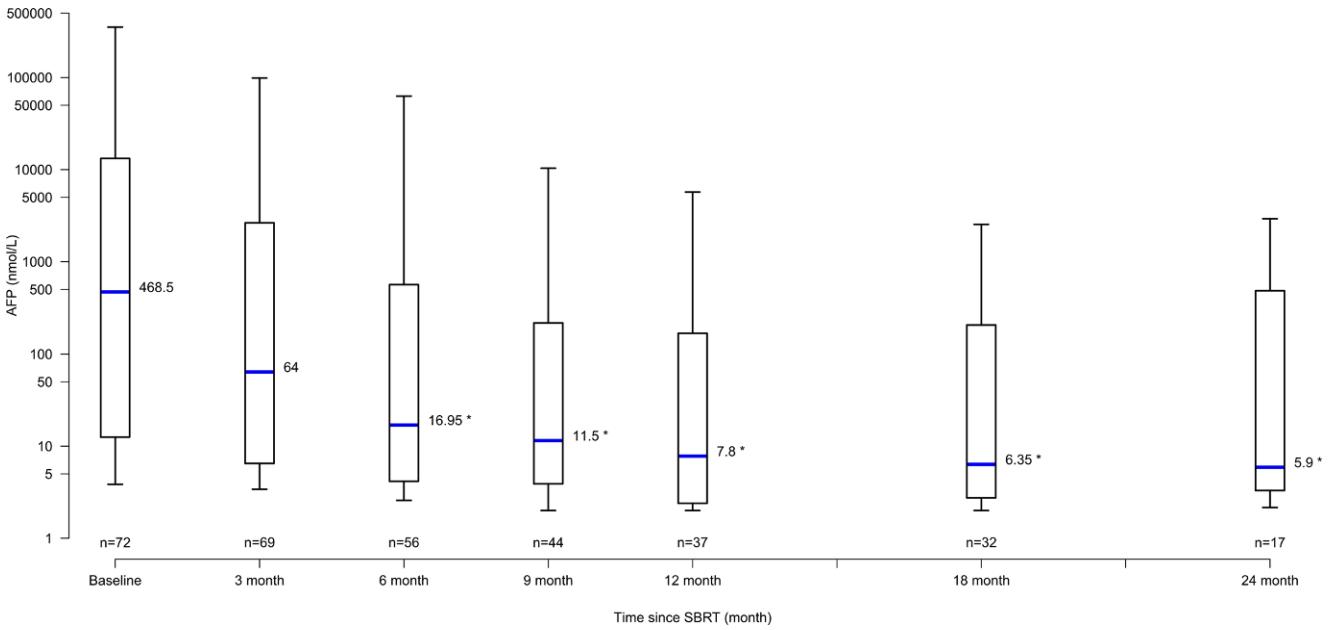

Fig. 2 Median serum α-fetoprotein (AFP) with time. *$p<0.05$ for difference from baseline using Wilcoxon signed-rank test. *Blue line* median, *thick box* 25th and 75th percentiles (i.e., the interquartile range), *error bar* 5th and 95th percentiles

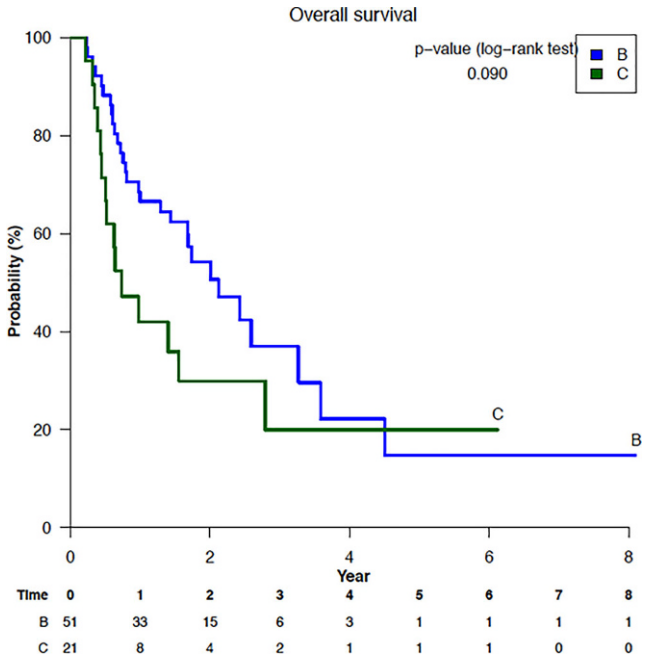

Fig. 3 Overall Survival of patients with BCLC stage B (*blue*) versus stage C (*green*) disease

sites (intra- and extra-hepatic progression in 10 patients and intra-hepatic in-field and out-of-field progression in 2 patients). At the time of progression, 21 patients (36.8%) were treated with further local therapies (TACE or radiofrequency ablation) and 24 patients (17.5%) received sorafenib.

On the other hand, 12 (16.7%) patients with treatment response were subjected to curative surgical resections. Among them, the median size of the initial tumor was 12.5 cm (range 8.7–19.2 cm) compared to 7.7 cm (range 3.6–11 cm) post-treatment. Median reduction of longest tumor diameter was 38.5% (range: 23–59.3%). All patients had margin-negative resection (R0) performed and one had pathological complete response (PCR). Among 12 patients, 83.3% ($n=10$) were still alive at the time of analysis and median survival was not yet reached. We found a trend suggesting that the tumor size (>15 cm) is a poor predictive factor for subsequent resection after TACE and SBRT treatment (HR = 0.34, 95% CI = 0.06–1.27, $p=0.11$).

Toxicity

The toxicities of the combined treatment are summarized in Table 3. A total of 25 patients (34.7%) reported grade 3 or above toxicities after TACE, most commonly transient elevation of transaminase ($n=11$, 15.2%) and bilirubin ($n=9$, 12.5%), followed by pain ($n=3$, 4.2%). For SBRT toxicities, grade 3 or above adverse events occurred in 12 (16.9%) patients, while gastrointestinal (GI) toxicity was reported in 2 patients (2.8%). No radiation-induced liver disease (RILD) was reported. Grade 3 or above elevation of transaminase was found in 3 individuals (4.2%). A decline in CP class without intra-hepatic progression was found in 10.6, 12.8, and 0% at 3, 6, and 12 months after treatment, respectively. Treatment-related death occurred in one patient (1.4%). The patient had central tumor of 12.5 cm in size compressed on the biliary tree. He developed cholangitis and hepatic failure at around 3 months after completion of SBRT.

Table 2 Univariate and multivariate analysis of overall survival

	OS (UV) HR (95% CI)	*p*-value	OS (MV) HR (95% CI)	*p*-value
BCLC stage C vs. B	1.71 (0.91, 43.20)	0.09	–	–
Size of lesion (<15 cm vs.>15 cm)	3.24 (1.78, 5.91)	<0.001	2.88 (1.57, 5.29)	0.001
CP class A vs. B	0.63 (0.19, 2.05)	0.44	–	–
Vascular involvement	1.31 (0.68, 2.51)	0.42	–	–
ECOG 0–1 vs. 2	1.34 (0.64, 2.81)	0.44	–	–
Extra-hepatic disease	3.78 (1.62, 8.79)	0.002	4.46 (1.79, 11.12)	0.001
Multiple lesions	0.85 (0.47, 1.55)	0.60	–	–
Dose >50 vs. ≤50	0.66 (0.35, 1.26)	0.21	–	–
Post-treatment therapy	0.42 (0.23, 0.76)	0.004	0.33 (0.18, 0.64)	0.001

HR hazard ratio, *BCLC* Barcelona Clinic Liver Cancer system, *PVT* portal vein thrombosis, *CP* Child–Pugh, *ECOG* Eastern Cooperative Oncology Group performance score

Table 3 Summary of the grade 3 or above acute toxicities

	TACE			SBRT		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
All	23 (31.9%)	2 (2.8%)	0 (0%)	12 (16.7%)	1 (1.4%)	1 (1.4%)
Fatigue	0	0	0	0 (0%)	0 (0%)	0 (0%)
Elevation of transaminase	9	2	0	3	0	0
Bilirubin	9	0	0	6	1	0
Albumin	0	0	0	1	0	0
Platelet	1	0	0	4	1	0
WCC	1	0	0	3	0	0
Hemoglobin	2	0	0	4	0	0
Nausea and vomiting	1	0	0	0	0	0
RILD	NA	NA	NA	0	0	0
Cholangitis	0	0	0	0	0	1
Gastritis/ulcer	0	0	0	1	0	0
Pain	3	0	0	0	0	0
Hepatic failure	0	0	0	1	0	1
Fever	2	0	0	0	0	0
Deterioration of CP without progression						
CP score 3 month	14/66 (21.2%)					
CP class 3 month	7/66 (10.6%)					
CP score 6 month	10/39 (25.6%)					
CP class 6 month	5/39 (12.8%)					
CP score 12 month	3/23 (13%)					
CP class 12 month	0/23 (0%)					

RILD radiation-induced liver disease, *CP* Child–Pugh, *WCC* White cell counts, *TACE* trans-arterial chemoembolization, *SBRT* Stereotactic body radiotherapy

Discussion

This study is one of the few reports to evaluate combined TACE with SBRT as initial treatment in advanced stage HCC patients. Compared to previous reports [22–25], most patients in this study had advanced disease and heavy tumor load. The median tumor size was 11.2 cm, and 25% of tumors had vascular involvement. Combined TACE plus SBRT demonstrated promising anti-tumor activity in this population, with a 1-year local control rate of 93.6% and an objective response rate (ORR) of 68%.

Patients receiving TACE often required repeated sessions, although the benefit of scheduled repeated TACE over on-demand TACE remains controversial [26]. In the work by Terzi et al. [27], only 40% of patients required a second session of trans-arterial treatment after initial TACE.

According to our institutional protocol, no scheduled treatment was given unless disease progression occurred, to spare the patients from treatment-associated toxicity. In this series, TACE was given once prior to SBRT in 90% of the patients, and additional sessions of TACE were given in 26% of the patients. Among 55 patients with BCLC B disease, such a treatment approach resulted in a tumor response rate of 73.9%, which compared favorably with the 17–62% of TACE alone [28]. The response to TACE is usually worse in large tumors [29], but in the present series, among 44 evaluable patients with a tumor diameter >10 cm, an objective response was seen in 26 individuals (59%). For the survival outcome, the median OS was 25.7 months (95% CI, 16.9–38.7 months), which appears to be better than the historical results of 6–19.4 months by TACE alone in similar stage [6, 30]. The PFS of 9.1 months (95% CI, 7.2–19.8 months) also compared favorably to the historical results of 3–9 months by TACE alone [6].

In a previous meta-analysis, TACE plus radiotherapy was associated with better survival than TACE alone in unresectable HCC patients [31]. Furthermore, TACE plus SBRT was associated with significantly better OS than SBRT alone in the retrospective series of 127 HCC patients with size >5 cm [25]. Our findings add to the growing body of evidence that the combined approach provides therapeutic advantages over either TACE or SBRT alone.

Radioembolization using yttrium-90 (Y90)-tagged glass (TheraSpheres, MDS Nordion, Ottawa, Canada) or resin (SIR-Spheres, Sirtex Medical, Lane Cove, Australia) microspheres represent another option in this patient population [32, 33]. In the study by Salem et al. including 291 patients with a median tumor size of 7 cm, Y90 therapy was associated with response rate of 42% and time-to-progression of 7.9 months, which is at least comparable to that of TACE [33]. In the other recent phase II study including relatively small tumors (range from 2.3 to 3.7 cm for largest tumor size), Salem et al. demonstrated significantly better time-to-progression with Y90 radioemobilization than TACE (>26 months vs. 6.8 months) [34]. Whether radioembolization will result in similar local control to the combined treatment of TACE with SBRT, in particular in large tumors as in the present study, remains unclear and warrants further investigations.

For patients with BCLC stage C disease, the benefit of local therapy remains controversial [35] and few data are available on TACE plus SBRT in this population. In this study among 21 patients, the tumor response of 55% was significantly better than that of the sorafenib series, albeit with a similar OS of 8.9 months and PFS of 4 months [12, 13]. The improved local control did not translate into better survival in this population with a high competing risk of distant progression; out-field failure represented the predominant mode of progression and cause of death. Further analyses revealed that patients without extra-hepatic disease had better OS than those with distant metastases (11.5 months versus 6 months, $p < 0.04$), signaling that the combined local therapy may improve outcome if the disease remains within liver parenchyma; however, the results need to be interpreted in caution given the small sample size.

To date, there is no effective down-staging treatment for unresectable HCC patients. In this study, 12 (16.7%) individuals were able to receive curative resections after significant downsizing of tumor by TACE plus SBRT; all patients had margin-negative resection performed, and one individual with an initial tumor of 10 cm had achieved PCR. These findings provide preliminary evidence to support combined TACE and SBRT as down-staging treatment of unresectable HCC. We hypothesized that the favorable tumor response of the combined approach may render more patients suitable for curative resections. However, our analysis was retrospective and came from a single institution; also, the resectability criteria and surgical technique vary among different institutions. Therefore, our findings should not be generalized beyond this study population.

There is no size limit for a lesion in our protocol. Our analysis demonstrated that tumor size >15 cm ($n = 20$) is a significant poor prognostic factor, with a median OS of 7.2 months compared to 28.6 months for tumor size ≤15 cm ($p < 0.001$, HR 2.88). Despite the combined therapy can effectively induce tumor shrinkage, patients with advanced disease were often found to develop out-field progression shortly and resulting in limited survival. Based on this observation, the role of combined TACE plus SBRT seems to be limited in this population with short life expectancy. In the ongoing RTOG 1112 trial, patients with HCC > 15 cm were considered to be ineligible for the study [36]. Patients with large HCC often complain of tumor-related symptoms, for example pain, anorexia, and fatigue. Radiotherapy using conventional techniques has been proven to be an effective and efficient way to improve patients' quality of life and control symptoms [37], and it may still be considered an appropriate local therapeutic approach for patients with huge tumor size.

There were no abnormal safety signals of combined TACE and SBRT demonstrated in the present series. The toxicity profile of merging two local therapies was similar to those of either treatment alone [6, 15, 16]. Treatment was well tolerated, with only 1 patient failing to complete the planned treatment. We observed a low rate of ≥ grade 3 GI toxicity (2.8%) and no cases of radiation-induced liver disease (RILD). CP score progression occurred in around 10% of individuals at 3 months and 6 months, which was similar to that observed in SBRT series [16]. Overall, the chemoembolization prior to SBRT did not result in unexpected acute or late toxicities.

In a previous meta-analysis, the addition of radiotherapy to TACE increased the incidence of liver enzyme elevation, raised bilirubin, and in particular gastro-duodenal ulcer (odd ratio OR: 12.8) [31]. However, most studies included in the review utilized conformal radiation. In this study, only 1 (1.4%) patient developed ≥3 gastric ulcer; the observed low incidence was consistent with other series using a stereotactic technique, which allows the delivery of highly conformal radiation to maximally spare the adjacent organs at risk, like stomach, duodenum, and uninvolved liver. Most treated HCC lesions were large in size, with median diameter of 11.2 cm and GTV from 41 to 4009 cc. Consequently, the uninvolved liver volume (liver – GTV volume) was relatively small. We have made several efforts to mitigate the liver toxicity. First, we prescribed a modest dose of radiation (median EQD2: 37.3 Gy_2); the dose was lower compared to other similar studies with less advanced tumor [22–25]. Secondly, a moderate dose of cisplatin, 40 mg, was utilized in TACE. Thirdly, an interval of median 3 weeks (median: 22 days, range: 10–66 days) was given after TACE to allow hepatic injuries to recover before SBRT. Finally, every hepatitis B carrier had preemptive anti-viral therapy prescribed.

Despite the fact that most patients were monitored and their data were collected in a prospective manner according to institutional protocol, we cannot entirely eliminate the intrinsic bias of a retrospective design. The single-arm design and short follow-up time also posed a limitation to the robustness of the findings. Furthermore, it was a mono-institutional series: our SBRT protocol adapts the radiation dose according to the dose constraints of organs at risk and allows patients to receive 5–10 fractions of radiation, which is not a common practice around the world. It is also worth noting that our response assessment followed the RECIST v1.1 criteria, which show poor concordance with the newer modified RECIST criteria that take into account tumor viability. Oldrini et al. showed higher rate of CRs was observed using mRECIST v1.1 criteria compared to RECIST v1.1 (57% vs. 20% at 3 months and 91.4% versus 41.6% at 12 months) [38]. Although mRECIST and other criteria such as the EASL (European Association for the Study of Liver Diseases) may be accurate for ablative, embolic, or system therapies, their application to SBRT remains unclear [39, 40]. Additionally, most of our patients were hepatitis B carriers. Further studies and parameters are needed to evaluate such a treatment in a Western population, where hepatitis C and alcoholism are the most frequent etiologies of HCC [41].

In conclusion, our experience suggested that with appropriate patient selection, judicious prescription of treatment, and advancement of radiotherapy technique, combined TACE and SBRT could be a safe and effective initial therapy in patients with unresectable BCLC B–C HCC. However, based on our data, such an approach may not be suitable for patients with large tumors (>15 cm) or extra-hepatic disease. Further trials are warranted to evaluate such treatment prospectively, preferably in the randomized setting to compare with the current standard of care, TACE and sorafenib.

Conflict of interest C.L. Chiang, M.K.H. Chan, C.S.Y. Yeung, C.H.M. Ho, F.A.S. Lee, V.W.Y. Lee, F.C.S. Wong, and O. Blanck declare that they have no competing interests.

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