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Survival Outcome Analysis of Stereotactic Body Radiotherapy and Immunotherapy (SBRT-IO) versus SBRT-Alone in Unresectable Hepatocellular Carcinoma

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Keywords
Hepatocellular carcinoma · Stereotactic body radiotherapy · Immunotherapy

Abstract

Introduction: While combination of stereotactic body radiotherapy (SBRT) and immunotherapy are promising, their efficacy and safety have not been compared with SBRT-alone in patients with unresectable hepatocellular carcinoma (HCC). ***Methods:*** This retrospective study included 100 patients with nonmetastatic, unresectable HCC in two hospitals. Eligible patients had tumor nodules ≤3 and Child-Pugh liver function score of A5 to B7. Seventy patients received SBRT-alone, and 30 patients underwent combined SBRT and immunotherapy (SBRT-IO). Overall survival (OS), time to progression (TTP), overall response rate (ORR), and toxicity were analyzed. We adjusted for the potential confounding factors using propensity score matching. ***Results:*** The median tumor size was 7.3 cm (range, 2.6–18 cm). Twenty-five (25%) of patients had vascular invasion. Before propensity score matching, the 1-year and 3-year OS rate was 89.9% and 59.8% in the SBRT-IO group and 75.7% and

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42.3% in SBRT-alone group (p = 0.039). After propensity score matching (1:2), 25 and 50 patients were selected from the SBRT-IO and SBRT-alone group. The 1-year and 3-year OS was 92.0% and 63.9% in the SBRT-IO group versus 74.0% and 43.3% in the SBRT-alone group (p = 0.034). The 1-year and 3-year TTP was better in SBRT-IO group (1-year: 68.9% vs. 58.9% and 3-year: 61.3% vs. 32.5%, p = 0.057). The ORR of 88% (complete response [CR]: 56%, partial response [PR]: 22%) in SBRT-IO arm was significantly better than 50% (CR: 20%, PR: 30%) in the SBRT-alone arm (p = 0.006). Three patients (12%) developed ≥grade 3 immune-related treatment adverse events (n = 2 hepatitis, n = 1 dermatitis) leading to permanent treatment discontinuation. ***Conclusion:*** Adding immunotherapy to SBRT resulted in better survival with manageable toxicities. Prospective randomized trial is warranted.

Introduction

Hepatocellular carcinoma (HCC) ranks the second in cancer-related death and its incidences are increasing globally [1]. Surgical resection and liver transplantation are preferred, but only 30% of patients are eligible for curative treatment at presentation [2]. Majority of patients presented in unresectable disease. The standard of care of trans-arterial chemoembolization (TACE) or systemic therapy was associated with modest survival improvement [3–5].

Stereotactic body radiotherapy (SBRT) has emerged as a promising local treatment modality of HCC [6]. Studies have demonstrated the efficacy and safety of SBRT as a definite treatment in early-stage HCC [7, 8]. Evidence also showed the feasibility of SBRT in unresectable HCC with multifocal disease, large size tumor, or macrovascular invasion (MVI). Several retrospective or prospective series showed promising local control (LC) rates [9, 10]. However, out-of-field metastasis remains a serious problem in using SBRT to treat this patient population [9, 10]. Patients often develop intrahepatic or distant dissemination even if radiation can ablate the tumor and tumor thrombi. It is therefore rational to combine SBRT with systemic therapy in unresectable HCC.

Preclinical data showed that SBRT could modulate the tumor micro-environment, prime the immune system, and work synergistically with the checkpoint inhibitors [11, 12]. Emerging studies have demonstrated the promising efficacy and manageable safety profile of combined SBRT and immunotherapy [13–15]. Our pilot studies showed that the addition of anti-PD-1 therapy to SBRT provided durable out-of-radiation field control with a complete response (CR) rate of 50% [16, 17]. A phase II trial by our group demonstrated the favorable survival outcomes in patients with unresectable HCC treated by a novel combination of TACE, SBRT followed by anti-PD-L1 antibody [18]. While combined SBRT and immunotherapy (SBRT-IO) is promising, to date, there are no comparative study to evaluate the benefits of adding immunotherapy to SBRT. Thus, we conducted a propensity score matching analysis to compare the survival, LC, and safety of SBRT-IO combination versus SBRT-alone in patients with unresectable HCC.

Methods and Materials

This retrospective study included 100 patients with nonmetastatic, unresectable HCC who were diagnosed and treated at Queen Mary Hospital and Tuen Mun Hospital between December 2016 and March 2022. Diagnosis was confirmed by histopathology or radiological criteria specified in international guidelines [19]. In both institutions, HCC patients were evaluated in a multi-disciplinary team (MDT) comprised of hepatobiliary surgeons, oncologists, and radiologists. Both centers followed a unified treatment protocol in patient selection, radiotherapy planning, radiotherapy dose prescription and delivery, and patient follow-up.

All consecutive patients met the SBRT eligibility criteria per protocol were retrieved from a prospectively collected database for analysis: (1) HCC were classified as unresectable after a MDT review either because (a) R0 resection not feasible, (b) remnant liver volume <30% in non-cirrhotic patients or 40% in cirrhotic patients, or/and indocyanine green (ICG) test >15%, (c) Barcelona Clinic Liver Cancer (BCLC) stage B and up-to-seven out, or (d) BCLC stage C; (2) tumor nodules ≤3; (3) a minimum of 700 mL of uninvolved liver; (4) a Child-Pugh score of A5 to B7; (5) absence of extrahepatic metastasis, ascites, or encephalopathy; (6) Eastern Cooperative Oncology Group (ECOG) performance status 0–2; (7) adequate liver, renal, and bone marrow functions defined as hemoglobin ≥9 g/dL, absolute neutrophil count ≥1,500/μL, total bilirubin ≤2.0 × upper limit of normal (ULN), alanine transaminase (ALT) ≤3 × ULN, international normalized ratio (INR) ≤1.6, and calculated creatinine clearance ≥45 mL/min, and (8) no prior systemic therapy.

Patients with unresectable HCC treated with SBRT were offered the option of adding immunotherapy after radiation, based on the rationale stated previously. The patients were fully informed about the potential advantages and risks. The final treatment depended on patient's decision. All patients provided written, informed consent for therapeutic procedures. The study was approved by the Institutional Ethics Committee (CIRB-2023-001-2).

Treatment

For SBRT planning, patients were immobilized via a vacuum foam bag (Vac-LokTM; MEDTEC, IA, USA). Imaging was performed on the inhale breath-hold contrast computed tomography (CT) or four-dimensional CT. GTV was defined as tumor focus that was visualized on contrast imaging. No margin was added to form the clinical target volume (CTV). The individualized PTV margins were formulated to compensate the respiratory motion and set-up errors. Cone beam CT was acquired on board before

each treatment. The largest tumor was selected as index lesion of SBRT, while maximum three nodules were allowed provided that the liver tolerance dose can be met. The total dose of 25–45 Gy in five fractions was prescribed per protocol. The prescription isodose should encompass 95% of PTV. The final dose was determined such that a maximum tumoricidal dose could be delivered to tumors while respecting the tolerance dose of organ at risk (OAR) as detailed in the appendix (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000533425).

For patients in SBRT-IO arm, intravenous nivolumab (3 mg per kg) was started at 14 days (+/−3 days) after the completion of SBRT. Nivolumab was then given every 2 weeks until development of grade ≥3 immune-related adverse events (irAEs), progression, or patient's refusal. On the other hand, if radiological CR achieved or tumor became amendable to curative treatment, nivolumab was also stopped.

Assessment and Follow-Up

All patients underwent clinical evaluation, liver function testing, and abdominal CT scan or magnetic resonance imaging (or both) at baseline, every 12 weeks in the first 2 years after completion of SBRT, and every 4–6 months afterward. Chest imaging was performed at baseline, every 6 months thereafter or if there was clinical suspicious. An independent radiologist (K.C.), who blinded to the clinical histories of patients, used modified Response Evaluation Criteria in Solid Tumours (mRECIST) and Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) to evaluate the treatment response.

Patients were evaluated for any treatment-related adverse events (TRAEs) at 1 and 3 months and every 3 months thereafter in the SBRT-alone arm. For patients in SBRT-IO arm, patients were evaluated every 2 weeks during immunotherapy, 1 and 3 months upon completion of immunotherapy, and every 3 months afterward. Toxicity as measured by Common Terminology Criteria for Adverse Events (CTCAE) version 4.01.

Clinical endpoints were evaluated included the following: (1) overall survival (OS), defined as the time between the SBRT start date and the death from any cause; (2) time to progression (TTP), defined as time from SBRT to first documented PD per mRECIST (3) LC, defined as progressive disease or new enhancement within or at the margin of the treatment field (PTV + 1 cm); (4) objective response rate (ORR), per mRECIST; (5) disease control rate (DCR), expressed as the percentage of patients that had a CR, partial response (PR), or stable disease ≥6 months; (6) toxicity as measured by CTCAE version 4.01; (7) incidence of Child-Pugh score progression by ≥2 [20]; (8) the percentages of patients had curative surgery done after successful downstaging. Hepatic resection was performed if R0 resection could be achieved with sufficient liver volume and function; radiofrequency ablation (RFA) was done if residual viable tumor was ≤3 cm; (9) pattern of disease progression; (10) radiological response per RECIST v1.1.

Statistical Analysis

Continuous variables were presented as medians and ranges. Comparison between the groups was carried out using the χ^2 or Mann-Whitney U test where appropriate. OS and FFP probabilities were generated with the Kaplan-Meier statistics. Cox proportional hazard regression model was used to determine independent prognostic factors. Statistical significance was defined as $p < 0.05$, and all the performed tests were two-tailed. Data were analyzed using R version 3.25 (Vienna, Austria).

Propensity score matching was used to reduce the potential confounding effect of treatment and selection bias, thereby creating a quasi-randomized experiment. Subsequently, a 2:1 ratio matching between the SBRT-alone and SBRT-IO groups was performed to maximize the propensity score match. Age, sex, tumor size, number of tumor nodule(s), BCLC stage, and vascular invasion were selected based on this score and calculated from baseline characteristics. The nearest-neighbor matching algorithm without replacement was used. The value of caliper was 0.30. The propensity scores are estimated with all variables described in Table 1 using a parsimonious logistic regression model.

Results

Patient Characteristics and Treatments

100 patients with HCC were identified and treated at Queen Mary Hospital and Tuen Mun Hospital during the period of December 2016 and March 2022. Before propensity score (PS) matching, 100 patients with 118 HCC tumors were included, of whom 70 patients with 80 HCC tumors were treated with SBRT-alone and 30 patients with 38 HCC tumors were treated with SBRT-IO. Baseline patient and tumor characteristics of the entire cohort and PS-matched cohorts are shown in Table 1.

Patients treated with SBRT-IO had a larger tumor with median size of 9 cm (range: 3.5–18 cm) versus 6.7 cm (range: 2.6–17.9 cm) ($p = 0.05$), higher incidence of MVI (40% vs. 18.6%, $p = 0.023$). After PS matching, there were no significant differences between two groups.

The median number of cycles of nivolumab received was 9 cycles (interquartile range, 5–12 cycles). The median duration of nivolumab was 4.2 months (interquartile range, 2.3–5.5 months). The median dose of SBRT prescribed was 30 Gy in 5 fractions (range: 25–45 Gy in 5 fractions) in both groups ($p = 0.408$).

OS and Time to Progression

Before the PS matching, median follow-up period in the SBRT-IO and SBRT-alone groups was 19.0 months (range: 2.5–59.6 months) and 24.1 months (range: 2.2–69.9 months), respectively. The 1-year, 2-year, and 3-year OS was 89.9%, 81.6%, and 59.8% in the SBRT-IO group and 75.7%, 51.3%, and 42.3% in the SBRT-alone group, respectively ($p = 0.039$). The median OS was not reached (range: 2.5–59.6 months) in SBRT-IO compared to 24.5 months (2.2–69.9 months) (Fig. 1a). The 1-year, 2-year, and 3-year rate of TTP was 65.3%, 65.3%, and 58.8% in the SBRT-IO group and 55.2%, 35.5%, and 24.4% in the SBRT-alone group, respectively ($p = 0.03$). The median TTP was 30.8 months (range: 2.6–59.6 months) in SBRT-IO versus 14.4 months (range: 0.3–69.9 months) in SBRT-alone (Fig. 1b).

Table 1. Baseline demographics and tumor characteristics of all patients

	Before propensity score matching			After propensity score matching		
	SBRT-alone (*N* = 70)	SBRT-IO (*N* = 30)	*p* value	SBRT-alone (*N* = 50)	SBRT-IO (*N* = 25)	*p* value
Age (median, range), years	70 (52–88)	72 (38–91)	0.718	69 (52–86)	73 (38–91)	0.157
Sex, *n* (%) (male)	54 (77.1)	26 (86.7)	0.275	41 (82.0)	21 (84.0)	0.829
Hepatitis B carrier, *n* (%)	50 (71.4)	20 (66.7)	0.634	37 (74.0)	15 (60.0)	0.215
ECOG 0–1, *n* (%)	45 (64.3)	21 (70.0)	0.580	34 (68.0)	16 (64.0)	0.729
Child-Pugh class A, *n* (%)	67 (95.7)	28 (93.3)	0.617	49 (98.0)	23 (92.0)	0.211
ALBI grade, *n* (%)			0.602			0.293
A	32 (45.7)	16 (53.3)		23 (46.0)	13 (52.0)	
B	37 (52.9)	13 (43.3)		27 (54.0)	11 (44.0)	
C	1 (1.4)	1 (3.3)		0 (0.0)	1 (4.0)	
Platelet, ($\times 10^9$)	162.5 (52–415)	214.5 (79–608)	0.094	167.5 (52–415)	205 (79–608)	0.213
INR	1.1 (1–3.7)	1.1 (0.9–1.5)	0.958	1.1 (1–1.3)	1.07 (0.9–1.5)	0.921
BCLC stage, *n* (%)			0.547			0.847
A	41 (58.6)	14 (46.7)		25 (50.0)	14 (56.0)	
B	7 (10.0)	4 (13.3)		6 (12.0)	3 (12.0)	
C	22 (31.4)	12 (40.0)		19 (38.0)	8 (32.0)	
Tumor number, *n* (%)			0.270			0.504
1	60 (85.7)	23 (76.7)		41 (82.0)	22 (88.0)	
2–3	10 (14.3)	7 (23.3)		9 (18.0)	3 (12.0)	
Reasons of unresectable			0.231			0.986
Inadequate liver remnant volume and/or poor ICG	44 (62.9)	14 (46.7)		27 (54.0)	14 (56.0)	
BCLC stage B and up-to-seven out	4 (5.7)	4 (13.3)		4 (8.0)	3 (12.0)	
BCLC stage C without extrahepatic spread	22 (31.4)	12 (40.0)		19 (38.0)	8 (32.0)	
Tumor size, cm	6.7 (2.6–17.9)	9 (3.5–18)	0.050	6.95 (2.6–14.2)	8.5 (3.5–15.6)	0.220
GTV volume (cc)	202 (16.5–2,246)	205 (4–1,828.4)	0.812	315 (19.9–1,718.2)	205 (4–1,817.8)	0.316
Vascular invasion, *n* (%)	13 (18.6)	12 (40.0)	0.023	13 (26.0)	8 (32.0)	0.585
AFP ≥200 ng/mL, *n* (%)	28 (40.0)	12 (40.0)	1.000	22 (44.0)	9 (36.0)	0.507
Median (range)	46.6 (2–161,947)	91.5 (3–499,988)		68.1 (2–161,947)	82 (3–46,388)	
SBRT dosage (median, range), Gy	30 (27.5–45)	35 (25–45)	0.336	30 (27.5–45)	30 (25–45)	0.408

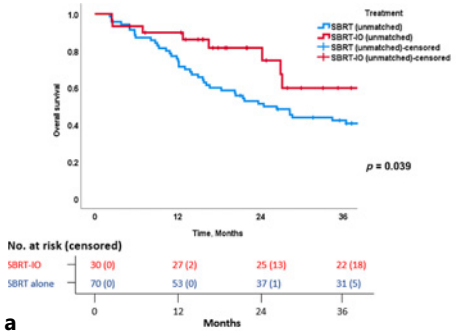
SBRT, stereotactic body radiotherapy; SBRT-IO, combined stereotactic body radiotherapy and immunotherapy; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin score; INR, international normalized ratio; BCLC, Barcelona Clinic Liver Cancer; GTV, gross tumor volume; AFP, alpha fetoprotein.

After PS matching, the median follow-up time in the SBRT-IO and SBRT-alone groups was 18.9 months and 25.4 months, respectively. The 1-year, 2-year, and 3-year OS of 92.0%, 82.1%, and 63.9% in SBRT-IO group was significantly better than 74.0%, 53.9%, and 43.3% in SBRT-alone group ($p = 0.034$) (Fig. 1c). The 1-year, 2-year, and 3-year of TTP of 68.9%, 68.9%, and 61.3% in SBRT-IO group was better than 58.9%, 40.5%, and 32.5% in the SBRT group ($p = 0.057$) (Fig. 1d).

Among 48 patients without MVI (BCLC stage A and B), the 1-year, 2-year, 3-year OS in SBRT-IO arm was 100%, 100%, 75% compared to 80.6%, 64.5%, 53.8% in SBRT-alone arm ($p = 0.061$). Among 27 patients with MVI (BCLC stage C), the 1-year, 2-year, and 3-year OS in SBRT-IO group was 75%, 46.9%, and 46.9% compared to 63.2%, 36.8%, and 26.3% in SBRT-alone group ($p = 0.300$) (online suppl. Table S2). The comparison of clinical outcomes of patients with BCLC stage A and B versus BCLC stage C was shown in online supplementary Table S3.

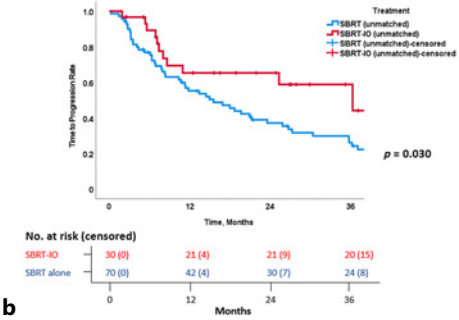
On multivariate analyses, SBRT-IO as treatment arm was associated with significantly better OS (hazard ratio [HR] = 0.375, range 0.156–0.903, $p = 0.029$). Other independent predictors of better OS included ALBI grade A (HR = 0.480, range 0.235–0.983, $p = 0.045$) and

	SBRT-IO (n = 30)	SBRT (n = 70)	p value
12-month rate, %	89.9% (72.0 – 96.6%)	75.7% (63.9 – 84.1%)	0.039
24-month rate, %	81.6% (61.1 – 92.0%)	51.3% (39.0 – 62.3%)	
36-month rate, %	59.8% (32.9 – 78.8%)	42.3% (30.5 – 53.6%)	
Median, months	NR (2.5 – 59.6 months)	24.5 months (2.2 – 69.9 months)	



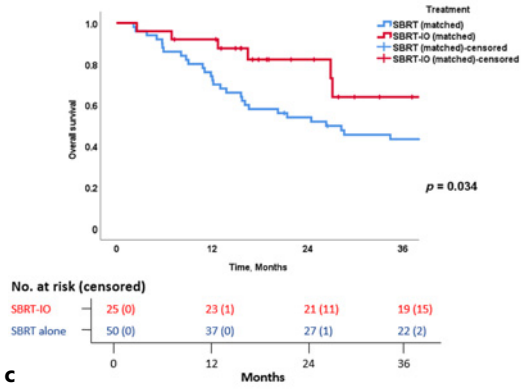
a

	SBRT-IO (n = 30)	SBRT (n = 70)	p value
12-month rate, %	65.3% (43.8 – 80.3%)	55.2% (42.5 – 66.2%)	0.030
24-month rate, %	65.3% (43.8 – 80.3%)	35.5% (24.0 – 47.1%)	
36-month rate, %	58.8% (35.8 – 76.0%)	24.4% (14.4 – 35.9%)	
Median, months	30.8 months (1.9 – 59.6 months)	14.4 months (0.3 – 69.9 months)	



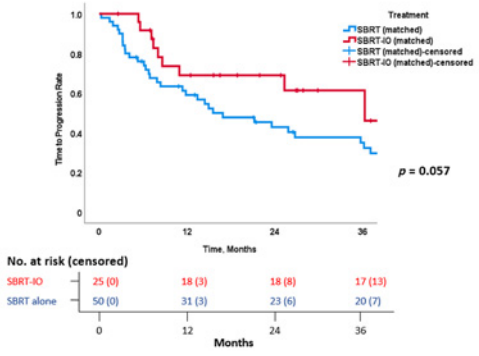
b

	SBRT-IO (n = 25)	SBRT (n = 50)	p value
12-month rate, %	92.0% (71.8 – 97.9%)	74.0% (59.5 – 84.0%)	0.034
24-month rate, %	82.1% (58.7 – 93.0%)	53.9% (39.1 – 66.6%)	
36-month rate, %	63.9% (33.3 – 83.3%)	43.3% (29.3 – 56.5%)	
Median, months	NR (2.6 – 59.6 months)	26.3 months (2.2 – 69.9 months)	



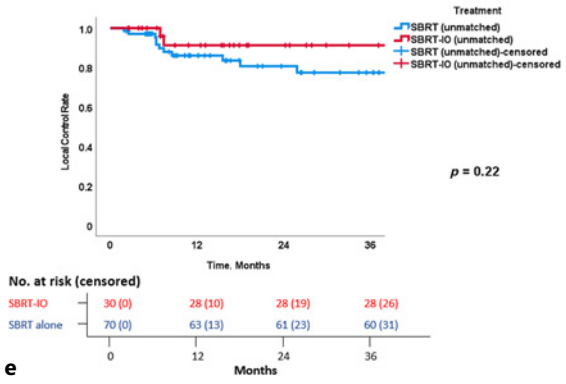
c

	SBRT-IO (n = 25)	SBRT (n = 50)	p value
12-month rate, %	68.9% (45.5 – 83.8%)	58.9% (43.7 – 71.3%)	0.057
24-month rate, %	68.9% (45.5 – 83.8%)	40.5% (26.3 – 54.3%)	
36-month rate, %	61.3% (35.9 – 79.1%)	32.5% (19.1 – 46.6%)	
Median, months	30.8 months (2.6 – 59.6 months)	15.0 months (0.3 – 69.9 months)	



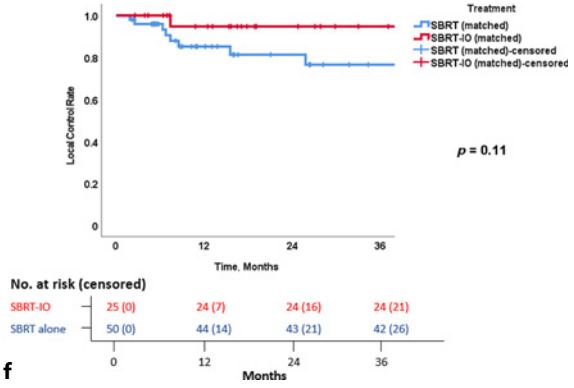
d

	SBRT-IO (n = 30)	SBRT (n = 70)	p value
12-month rate, %	91.3% (69.4 – 97.8%)	86.0% (73.9 – 92.7%)	0.22
24-month rate, %	91.3% (69.4 – 97.8%)	80.6% (66.4 – 89.3%)	
36-month rate, %	91.3% (69.4 – 97.8%)	77.4% (62.0 – 87.2%)	



e

	SBRT-IO (n = 25)	SBRT (n = 50)	p value
12-month rate, %	94.7% (68.5 – 99.2%)	85.2% (69.5 – 93.2%)	0.11
24-month rate, %	94.7% (68.5 – 99.2%)	81.3% (64.0 – 90.8%)	
36-month rate, %	94.7% (68.5 – 99.2%)	76.5% (57.2 – 88.0%)	



f

Fig. 1. Overall survival (**a**), progression-free survival (**b**), and local control rate (**c**) before propensity score matching (PSM). Overall survival (**d**), progression-free survival (**e**), and local control rate (**f**) after PSM.

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Table 2. Univariate and multivariate analyses of potential prognostic factors affecting overall and progression-free survival after propensity score matching

	Overall Survival						Time to Progression					
	UVA			MVA			UVA			MVA		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
For matched groups (*n* = 75)												
SBRT-IO versus SBRT	0.400	0.167–0.959	**0.040**	0.375	0.156–0.903	**0.029**	0.496	0.237–1.037	**0.062**			
Age (<60 vs. ≥60 years)	0.672	0.206–2.187	0.509				1.687	0.709–4.010	0.237			
Sex (male vs. female)	1.265	0.530–3.021	0.596				1.348	0.594–3.059	0.475			
Hepatitis B carrier (yes vs. no)	0.897	0.463–1.736	0.746				1.434	0.706–2.911	0.319			
ECOG (0–1 vs. 2)	1.187	0.617–2.287	0.607				1.594	0.818–3.109	0.171			
Child-Pugh class (A vs. B)	1.131	0.271–4.720	0.866				0.805	0.194–3.346	0.765			
ALBI grade (A vs. B)	0.348	0.178–0.680	**0.002**	0.480	0.235–0.983	**0.045**	0.572	0.311–1.051	**0.072**			
Portal vein invasion (yes vs. no)	1.433	0.728–2.823	0.298				1.163	0.585–2.313	0.666			
BCLC stage (A vs. C)	0.367	0.179–0.755	**0.006**				0.495	0.241–1.018	0.056			
BCLC stage (B vs. C)	0.490	0.143–1.682	0.257				0.714	0.235–2.165	0.551			
Tumor number (*n* = 1 vs. 2–3)	0.599	0.273–1.315	0.202				0.424	0.206–0.871	**0.019**			
Tumor size (<10 cm vs. ≥ 10 cm)	0.581	0.299–1.130	0.110				1.063	0.509–2.220	0.870			
AFP (<200 vs. ≥200 ng/mL)	0.579	0.311–1.079	**0.085**	0.427	0.219–0.835	**0.013**	0.466	0.256–0.851	**0.013**	0.319	0.168–0.604	<**0.001**
Treatment response												
(CR vs. SD + PD)	0.037	0.009–0.157	<**0.001**	0.036	0.008–0.161	<**0.001**	0.122	0.055–0.270	<**0.001**	0.086	0.037–0.201	<**0.001**
(PR vs. SD + PD)	0.435	0.221–0.858	**0.016**	0.554	0.273–1.125	0.102	0.190	0.086–0.421	<**0.001**	0.165	0.074–0.371	<**0.001**

SBRT, stereotactic body radiotherapy; SBRT-IO, combined stereotactic body radiotherapy and immunotherapy; ECOG, Eastern Cooperative Oncology Group; INR, international normalized ratio; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; CI, confidence interval.

Table 3. The best mRECIST and RECIST v1.1 response of the matched SBRT and SBRT-IO patients

	Matched SBRT,[#] *N* (%)	Matched SBRT-IO, *N* (%)	*p* value
mRECIST			
Best response rate, *n*, % (95% CI)			<0.001
CR, *n*, % (95% CI)	10, 20.0 (10–33.7)	14, 56.0 (34.9–75.6)	
PR, *n*, % (95% CI)	15, 30.0 (17.9–44.6)	8, 32.0 (15.0–53.5)	
SD, *n*, % (95% CI)	9, 18.0 (8.6–31.4)	3, 12.0 (2.6–31.2)	
PD, *n*, % (95% CI)	15, 30.0 (17.9–44.6)	0, 0.0	
Overall response rate (CR + PR), *n*, % (95% CI)	25, 50.0 (35.5–64.5)	22, 88.0 (68.8–97.4)	0.006
Disease control rate (CR + PR + SD ≥ 6 months), *n*, % (95% CI)	33, 66.0 (51.2–78.8)	22, 88.0 (68.8–97.4)	0.121
RECIST 1.1			
Best response rate, *n*, % (95% CI)			0.009
CR, *n*, % (95% CI)	1, 2.0 (0–10.7)	0, 0.0	
PR, *n*, % (95% CI)	18, 36.0 (22.9–50.8)	17, 68.0 (46.5–85.1)	
SD, *n*, % (95% CI)	15, 30.0 (17.9–44.6)	8, 32.0 (15–53.5)	
PD, *n*, % (95% CI)	15, 30.0 (17.9–44.6)	0 (0.0)	
Overall response rate (CR + PR), *n*, % (95% CI)	19, 38.0 (24.7–54.8)	17, 68.0 (46.5–85.1)	0.017
Disease control rate (CR + PR + SD ≥6 months), *n*, % (95% CI)	33, 66.0 (51.2–78.8)	22, 88.0 (68.8–97.4)	0.121
Patients with curative surgery done, *n*, % (95% CI)	5, 10.0 (3.3–21.8)	4, 16.0 (4.5–36.1)	0.451

SBRT, stereotactic body radiotherapy; SBRT-IO, combined stereotactic body radiotherapy and immunotherapy; mRECIST, modified response evaluation criteria in solid tumors; RECIST v1.1, response evaluation criteria in solid tumors version 1.1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; *N*, number of patients; DOR, duration of response. [#]1 subject in the matched SBRT cohort did not have follow-up scan for tumor reassessment.

AFP <200 ng/mL (HR = 0.427, range 0.219–0.835, p = 0.013). Of note, treatment response is an independent predictor of survivals (for CR: HR = 0.036, range 0.008–0.161, $p < 0.001$; for PR: HR = 0.554, range 0.273–1.125, p = 0.102) (Table 2). Among 24 patients achieved CR, the 1-year, 2-year, and 3-year OS rates were 100%, 100%, and 93.8%, respectively (online suppl. Fig. S1).

LC and Response Rates

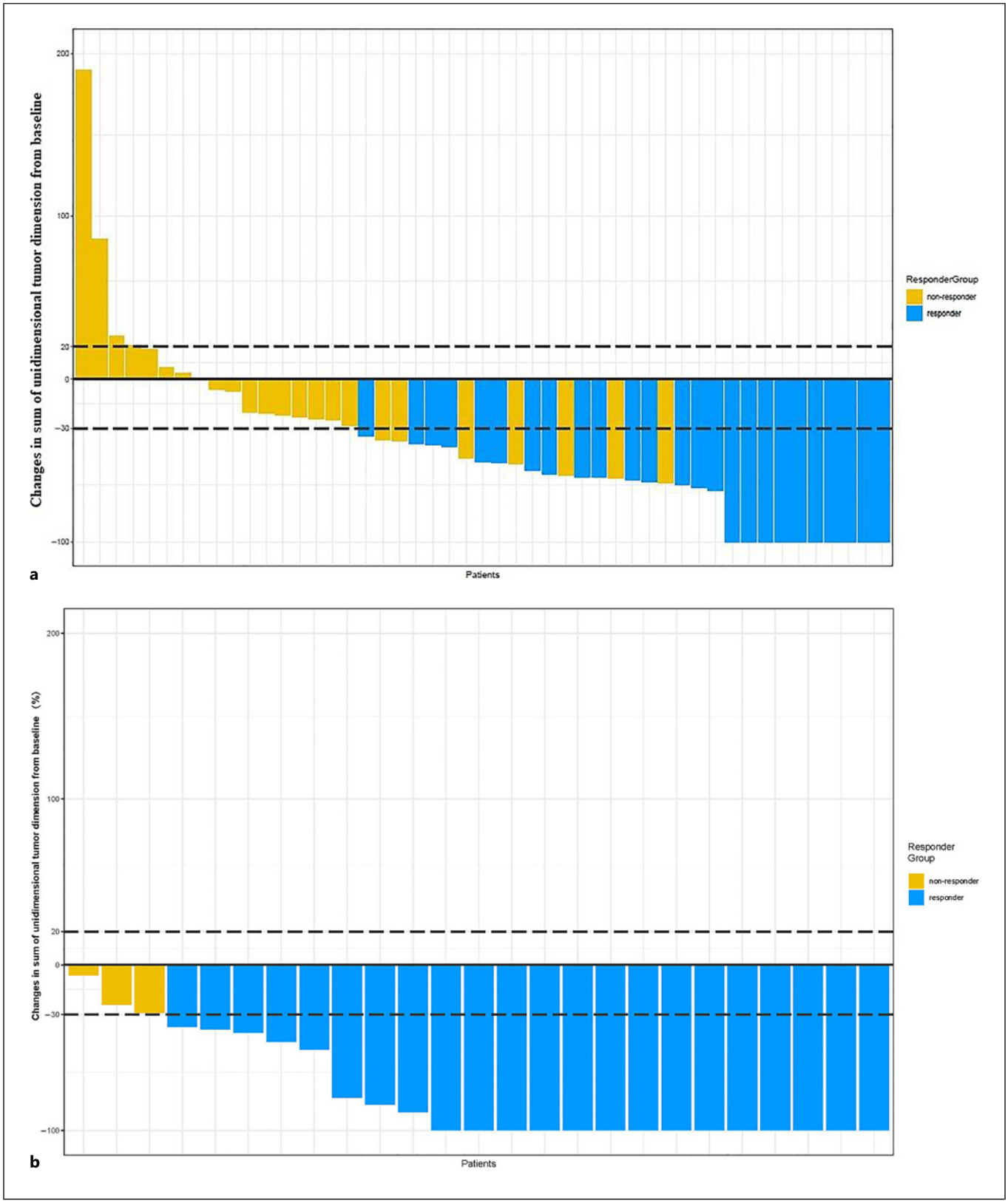
Before the PS matching, the 1-year, 2-year, and 3-year LC rates were all 91.3% in SBRT-IO group and 86.0%, 80.6%, and 77.4% in SBRT-alone group (p = 0.22) (Fig. 1e). After the PS matching, the 1-year, 2-year, 3-year LC rates were all 94.7% in the SBRT-IO group. The 1-year, 2-year, and 3-year LC rates were 85.2%, 81.6%, and 76.5%, respectively, in the SBRT group (p = 0.11) (Fig. 1f).

The ORR rate of SBRT-IO group per mRECIST was 88% with 14 CRs and 8 PRs, which was better than that of 50% in the SBRT-alone group (CRs = 10, and PRs = 15) ($p < 0.001$). There was also a trend suggesting better DCR in SBRT-IO group (88% vs. 66%, p = 0.121) (Table 3). Among 48 patients without MVI (BCLC stage A and B), the best ORR was 88.2% in SBRT-IO arm compared to 64.5% in SBRT-alone arm (p = 0.077). Among 27 patients with MVI (BCLC stage C), the OS was significantly better in SBRT-IO group (87.5% vs. 26.3%, $p < 0.001$) (online suppl. Table S2).

Figure 2 depicted that the changes of tumor diameters of target lesion(s) in SBRT-IO and SBRT-alone groups. Target lesion(s) regressed in 47 (81.0%) of 58 evaluable lesions in SBRT-alone group versus 29 (100%) of 29 lesions in SBRT-IO group (Fig. 2a, b; online suppl. Fig. S2). The best tumor response per RECIST v1.1 is also shown in Table 3. Both mRECIST and RECIST criteria correlated with OS and TTP of patients (online suppl. Table S4). Four patients (16%) in the SBRT-IO group had curative surgery (n = 2, resection, n = 2, RFA) performed after initial treatment response compared to 5 patients (10%) in the SBRT group (n = 4, resection, n = 1, RFA) (p = 0.451).

Failure Pattern and Subsequent Treatment

Online supplementary Table S5 listed the pattern of failure at 6 months, 12 months, 24 months, and 36 months after treatment. Overall, at 6 months and 12 months, there was no significant difference in terms of treatment failure rate and pattern of failure between 2 groups. SBRT-IO was associated with less treatment failure at 24 months (28% vs. 56%, p = 0.022) and 36 months (32% vs. 62%, p = 0.014) (online suppl. Fig. S3a). There was a trend suggested better in-field control (4% vs. 14%, p = 0.186) and reduced distant metastases (8% vs. 24%, p = 0.094) in SBRT-IO arm (online suppl. Fig. S3b, c). Of note, 4 patients (8%) received sorafenib



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(For legend see next page.)

Table 4. Treatment related adverse event (TRAE) and Child-Pugh score progression of matched SBRT versus matched SBRT-IO

	SBRT (N = 50)		SBRT-IO (N = 25)		p value
	any grade	grade 3–4	any grade	grade 3–4	
Treatment-related AEs		9 (22.5)		7 (35)	0.302
AEs led to discontinuation	0 (0)	0 (0)	4 (20)	4 (20)	0.003
Treatment-related death	0 (0)	0 (0)	0 (0)	0 (0)	---
Hemoglobin	23 (57.5)	0 (0)	12 (60)	0 (0)	0.853
Leukocytes	8 (20)	0 (0)	3 (15)	0 (0)	0.637
Platelet	24 (60)	4 (10)	12 (60)	0 (0)	1.000
Bilirubin	10 (25)	1 (2.5)	4 (20)	1 (5)	0.666
AST/ALT	22 (55)	2 (5)	16 (80)	4 (20)	0.058
Nausea and vomiting	9 (22.5)	0 (0)	2 (10)	0 (0)	0.238
Diarrhea	1 (2.5)	0 (0)	3 (15)	0 (0)	0.067
Appetite lost	4 (10)	0 (0)	2 (10)	0 (0)	1.000
Fatigue	12 (30)	1 (2.5)	9 (45)	1 (5)	0.251
Fever	1 (2.5)	0 (0)	2 (10)	0 (0)	0.209
Weight loss	3 (7.5)	0 (0)	1 (5)	0 (0)	0.714
Pain	9 (22.5)	1 (2.5)	2 (10)	0 (0)	0.238
Rash	0 (0)	0 (0)	4 (20)	0 (0)	0.003
Pruritus	1 (2.5)	0 (0)	3 (15)	1 (5)	0.067
Progression of CP score ≥2					
3 months	7/45 (15.6)		2/24 (8.3)		0.396
6 months	5/40 (12.5)		1/22 (4.5)		0.311
12 months	2/29 (6.9)		1/15 (6.7)		0.977

Values are given as n (%). SBRT, stereotactic body radiotherapy; SBRT-IO, combined stereotactic body radiotherapy and immunotherapy; AEs, adverse events; AST, aspartate transaminase; ALT, alanine transaminase; CP, Child-Pugh. The incidence of only toxicities ≥5% is shown.

and 10 patients (20%) received TACE after treatment failure in the SBRT group, while 3 patients (12%) received multiple lines of systemic therapy in the SBRT-IO group (online suppl. Table S6).

Adverse Events

There was no significant difference in the rates of ≥grade 3 TRAEs between 2 arms. However, SBRT-IO was associated with significantly more treatment discontinuation due to AE (20% vs. 0%, p = 0.003) due to ≥grade 3 hepatic enzymes (AST/ALT) elevation. Otherwise, there was no difference in ≥grade 3 treatment-related AE between two groups. Rash and pruritus are more common in patients treated with SBRT-IO. No patients developed classic radiation-induced liver disease. The incidence of CP score progression ≥2 at 3 months, 6 months, and 12 months were similar. No treatment-related death was reported in both groups (Table 4).

Discussion

To the best of our understanding, this was the first study to compare the clinical outcomes of SBRT-IO combination versus SBRT-alone in patients of unresectable HCC. Our results showed that adding immunotherapy was associated with a markedly longer TTP and better ORR, which was translated into OS advantage. Noteworthy, 56% of patients treated with SBRT-IO achieved radiological CR that the remission was durable with 3-year OS rate of around 90%.

In our study, adding anti-PD-1 therapy resulted in significantly markedly longer TTP (median: 30.8 vs. 15.6 months and 3-year: 61.3% vs. 32.5%, p = 0.057) by reducing the incidences of out-field intrahepatic progression (28% vs. 40%) and distant metastases (8% vs. 24%). The benefits have been observed in both patients with and without MVI. Previous study suggested the

Fig. 2. Waterfall plot. Percentage changes in sum of unidimensional tumor dimension from baseline in individual patients of (**a**) matched SBRT arm per mRECIST (49 patients with total 58 lesions [1 subject was not evaluable and 9 subjects had 2 irradiated lesions]), and (**b**) matched SBRT-IO arm per mRECIST (25 patients with total 29 lesions [2 subjects had 2 irradiated lesions, and 1 subject had 3 irradiated lesions]).

immuno-modulatory effect of SBRT enhance the effect of checkpoint inhibitor to eradicate the micro-metastases, which the phenomenon was known as "systemic therapy augmented by radiotherapy (STAR)" [21]. Similar encouraging results were reported in recent trials of combined radiation and immunotherapy. Among 23 patients with nonmetastatic unresectable HCC treated with combined Y90 radioembolization and nivolumab, the median OS, median PFS, and ORR was 20.1 months, 15.1 months, and 43.5%, respectively [22]. In START-FIT trial, among 33 patients with locally advanced HCC, the median OS, median PFS, and ORR was 30.3 months, 20.7 months, and 67%, respectively [18]. Among 7 patients in a phase I trial treated with SBRT followed by nivolumab and ipilimumab, the median OS, median PFS, and ORR was 41.6 months, 11.6 months, and 57%, respectively. Our results have supported the growing body of evidence on the promising efficacy of combined radiotherapy-immunotherapy approach in unresectable HCC population.

An individualized radiation dose-allocation strategy was adopted to treat large, multifocal, and macrovascular invasive HCC [9, 10, 23]. Pitfalls of this approach are that sizable lesions are more likely to receive non-ablative doses, and the radiation doses prescribed are heterogeneous. As a result, the LC of large-size lesion is comparatively worse. Pooled analyses showed that 2-year LC of HCC <5 cm was 87.1% compared to 66.3% in HCC ≥5 cm [24]. In current study, under the similar radiation doses, there was a trend toward better LC rate in the SBRT-IO arm. While the LC declined with time in SBRT-alone arm, the LC rate remains over 90% during the entire follow-up period in SBRT-IO arm (2-year: 94.7% vs. 81.3%; 3-year: 94.7% vs. 76.5%). Preclinical data suggested immunotherapy could sensitize the tumor to radiation so that similar LC could be achieved by lower radiation dose [25]. This is particularly important when treating locally advanced HCC with SBRT, as our study demonstrated; the radiation dose permitted is often limited by the tolerance of normal liver parenchyma. Notably, all the gross lesions have received radiation in our study, emerging data favored the comprehensive radiation of all gross diseases to improve the immune access of bulky lesions and increase the chance of successful priming of antitumor immune response [26].

The superior tumor response rate of SBRT-IO has a couple of implications. First, the achievement of tumor downsizing facilitated more patients had curative surgery performed (16% vs. 10%), which have contributed to the survival advantage. Second, previous studies demonstrated that treatment response is an independent predictive factor of survival [27, 28]. Similar findings were observed in our cohort. Notably, among 27 patients achieving radiological CR, the 3-year OS was 94.1%. The better ORR and CR rates achieved by SBRT-IO implied higher proportion of patients may derive survival benefit from treatment.

Emerging data showed that combined SBRT and molecular targeted agents are promising in patients with advanced HCC patients. In RTOG 1112 trial, SBRT followed by sorafenib was associated with improved median OS (15.8 months vs. 12.3 months) and median PFS (9.2 months vs. 5.5 months) compared to sorafenib alone [29]. Further investigation, preferably prospective trial, is therefore warranted to compare the outcomes of combined SBRT-IO against combined SBRT and targeted therapy in patients of unresectable HCC.

There were no safety concerns noted in the SBRT-IO combination when compared to SBRT or immunotherapy alone. Three patients (12%) in the SBRT-IO developed ≥grade 3 irAEs (n = 2, hepatitis, n = 1, dermatitis) leading to permanent discontinuation of treatment. This was consistent with that reported in previous checkpoint inhibitors studies in HCC patients [30–32]. All 4 patients had irAEs resolved with steroid and without long-term sequelae. Indeed, recent literatures suggested patients developed severe irAEs may associated with better long-term prognoses [33]. Both arms observed a similar rate of decline in CP score followed by delay in recovery, which could be attributed to the ongoing antitumor effect of radiotherapy and hepatocyte repopulation. Our findings indicated that adding anti-PD-1 therapy after SBRT neither exacerbate the degree of liver damage nor impact the recovery process.

However, some limitations merit discussion. First, this was a retrospective study with modest sample size; some intrinsic biases could not be fully eliminated by propensity score matching analysis. For example, the potential confounding effects of tumor volume or radiation dose could not be entirely eliminated in the current analysis. Second, it remains uncertain whether the mRECIST is the optimal method to assess treatment response in patients receiving radiation and its combination [32]. Nevertheless, we have analyzed clinical outcomes based on both RECIST v1.1 and mRECIST and showed that both criteria were correlated to patient survival. Third, the socioeconomic status (SES) of patients may confound their decision on whether adding immunotherapy after radiation. A charity funding program was in place to partially sponsor the immunotherapy for those with limited financial affordability, which may minimize the impact of SES on patients' decisions. Also, limiting the duration of immunotherapy to a certain duration should be considered. Lastly, there may be selection and management biases even a unified

treatment protocol was shared between two centers and patients were treated in the same period. Nevertheless, our study findings warranted further validation in prospective randomized setting.

Conclusion

Our findings showed that adding IO substantially enhanced the oncological effect of SBRT in unresectable HCC. These findings warranted further evaluation in a randomized control study.

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Statement of Ethics

The study was approved by the Institutional Ethics Committee, Hospital Authority, Hong Kong (CIRB-2023-001-2). Informed consent form was waived from the Institutional Ethics Committee approval given the retrospective nature of study. Also, SBRT-immunotherapy and SBRT-alone are part of the treatment options in our institutions. All the patients have written consent forms signed for the treatment received.

Conflict of Interest Statement

We declare no competing interests.

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Author Contributions

Chi Leung Chiang and Albert Chi Yan Chan conceived and designed the study. Chi Leung Chiang, Albert Chi Yan Chan, Francis Ann Shing Lee, Natalie Sean Man Wong, Cynthia Sin Yu Yeung, Winnie Wing Ning Yip, and Vince Wing Hang Lau contributed to patient recruitment and provision of study materials. Chi Leung Chiang, Francis Ann Shing Lee, Venus Wan Yan Lee, Ryan Lok Man Ho, and Albert Chi Yan Chan collected and assembled the data. Kenneth Sik Kwan Chan and John Ka Shun Fong performed data analysis. Chi Leung Chiang, Albert Chi Yan Chan, and Keith Wan Hang Chiu interpreted the data.

Chi Leung Chiang, Francis Ann Shing Lee, Kenneth Sik Kwan Chan, Venus Wan Yan Lee, Keith Wan Hang Chiu, Ryan Lok Man Ho, John Ka Shun Fong, Natalie Sean Man Wong, Winnie Wing Ling Yip, Cynthia Sin Yu Yeung, Vince Wing Hang Lau, Kwan Man, Feng Ming Spring Kong, and Albert Chi Yan Chan prepared and approved the manuscript.

All authors confirmed that they had full access and verification to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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