Efficacy of Stereotactic Body Radiation Therapy in Patients With Pd-1 Inhibitor–transarterial Chemoembolization Refractory Intermediate-stage Hepatocellular Carcinoma: a Retrospective Controlled Study

Yan-Jun Xiang

Eastern Hepatobiliary Surgery Hospital

Kang Wang

Eastern Hepatobiliary Surgery Hospital

Yi-Tao Zheng

The First Affiliated Hospital of Wenzhou Medical University

Shuang Feng

Eastern Hepatobiliary Surgery Hospital

Hong-Ming Yu

Eastern Hepatobiliary Surgery Hospital

Xiao-Wei Li

Eastern Hepatobiliary Surgery Hospital

Xi Cheng

Eastern Hepatobiliary Surgery Hospital

Yu-Qiang Cheng

Eastern Hepatobiliary Surgery Hospital

Wei-Jun Wang

Eastern Hepatobiliary Surgery Hospital

Jin-Kai Feng

Eastern Hepatobiliary Surgery Hospital

Ying-Yi Qin

Second Military Medical University

Li-Ping Zhou

Eastern Hepatobiliary Surgery Hospital

Yan Meng

Eastern Hepatobiliary Surgery Hospital

Jian Zhai

Eastern Hepatobiliary Surgery Hospital

Yun-Feng Shan

The First Affiliated Hospital of Wenzhou Medical University

Shu-Qun Cheng (✉ chengshuqun@aliyun.com)

Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai <https://orcid.org/0000-0001-6760-7470>

Research Article

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Abstract

Introduction:

Transarterial chemoembolization (TACE) combined with PD-1 inhibitor is a novel and effective combination therapy. However, there is currently a gap in subsequent treatment when patients are diagnosed with PD-1 inhibitors-TACE refractoriness.

Methods:

This retrospective cohort study included enrolled patients with intermediate stage HCC who were diagnosed with PD-1 inhibitor-TACE refractoriness between January 2019 and December 2020 in the Eastern Hepatobiliary Surgery Hospital and the First Affiliated Hospital of Wenzhou Medical University. They were divided into two cohorts, (1) those who switched from TACE combined with PD-1 to stereotactic body radiation therapy (SBRT) combined with PD-1 and (2) those who continued TACE combined with PD-1. Progression free survival (PFS), overall survival (OS), and tumor response were assessed in both groups after refractory to PD-1 inhibitors combined with TACE.

Results: Of the seventy-six patients included in this study, the median PFS was 19.6 months in the SBRT group (n=31) and 10.1 months in the TACE group (n=45, $p<0.05$). The SBRT group also had a significant higher OS than the TACE group ($p<0.05$). Objective response rate (ORR) and disease control rate (DCR) were also better in the SBRT group (ORR, 71.0% vs. 15.6%, OR=8.483, 95%CI 3.319-21.680, $P < 0.001$; DCR, 80.6% vs. 31.1%, OR=9.226, 95%CI 3.096-27.493, $P < 0.001$).

Conclusions: SBRT combined with PD-1 inhibitor improves PFS and OS in patients refractory to PD-1 inhibitor combined with TACE. Therefore, SBRT is recommended in case of failure of treatment with PD-1 inhibitors combined with TACE.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the fourth leading cause of cancer-related death worldwide[1]. Since patients with early-stage HCC are usually asymptomatic, approximately half of HCC patients are diagnosed at intermediate to advanced stages and cannot undergo radical treatment[2–5].

For patients with intermediate stage HCC, TACE is recommended as the standard treatment by many guidelines[6–9]. However, the efficacy of TACE alone is limited and some patients would be diagnosed as TACE refractory[10, 11]. Most guidelines recommend starting systemic therapy as soon as TACE refractoriness appears (defined as failure to achieve an objective response after two procedures)[6, 8, 9]. As a new systemic therapeutic drug, PD-1 inhibitor has synergistic effect with TACE[12, 13]. The ORR of patients who received TACE combined with PD-1 inhibitor therapy was 47.1%[14]. In other words, more

than half of the patients did not achieve an effective tumor response, and there is currently a lack of relevant reports regarding subsequent therapies for this subset of patients.

Stereotactic body radiotherapy (SBRT) is a newer treatment modality with evidence of promising local control for patients with HCC[15–17]. And for early and intermediate stage HCC patients, SBRT is a safe alternative to TACE and provides no inferior or even better local control and OS than TACE[18, 19].

Based on the above literature, we speculated that SBRT might be a reasonable alternative for patients with PD-1 inhibitor–TACE refractory. While there are no relevant reports available so far. We conducted this retrospective study to evaluate the efficacy and safety of SBRT in patients with PD-1 inhibitor–TACE refractory intermediate-stage hepatocellular carcinoma.

Methods

Patients

A retrospective study was conducted on consecutive HCC patients at the Eastern Hepatobiliary Surgery Hospital and the First Affiliated Hospital of Wenzhou Medical University from 2019 to 2020. This study was approved by the Institutional Ethics Committee of the Eastern Hepatobiliary Surgery Hospital of the main center. As patient identities were anonymized, the requirement for informed consent was waived by the Ethics Committees.

The inclusion criteria were patients with: (1) HCC diagnosed by histopathology, computed tomography (CT) or magnetic resonance imaging (MRI), (2) good liver function (Child-Pugh A or B7, score ≤ 7), (3) BCLC stage B, (4) received TACE combined with PD-1 inhibitor therapy, (5) PD-1 inhibitor refractoriness (defined as tumors that did not achieve an objective response as assessed by modified Response Evaluation Criteria in Solid Tumor (mRECIST) after 4 cycles of PD-1 inhibitor therapy), and (6) TACE-refractoriness. The exclusion criteria were patients with (1) previous other locoregional or systemic therapy, (2) recurrent HCC, (3) a history of other cancers, and (4) incomplete clinical data.

TACE and SBRT

TACE was performed as previously described[20]. Briefly, the tumor feeding artery was first identified by angiography, and after cannulation of the hepatic artery, doxorubicin hydrochloride, pirarubicin and lipiodol were injected through the catheter. Post TACE evaluation and follow-up were performed every 6-8 weeks.

SBRT was performed by CyberKnife® (Accuriy Cyber knife, VSI), with a total of 24–45 Gy in 3–5 fractions. The patients who received SBRT were first implanted with at least 3 gold fiducials inside or adjacent to the tumor under CT (Philips Brilliance CT Big Bore Oncology) guidance, and the gold fiducials were relatively stable and immobile after seven days, with localization simulated under CT. The images are subsequently transferred to the treatment planning system (TPS), and the target area was then delineated by a radiologist. A 2-5 mm marginal expansion of the gross tumor volume (defined as

radiologically evident gross disease) formed the planning target volume. And the physiatrist makes the treatment plan while defining normal tissue dose ranges. Dose constraints for organs at risk refer to the American Association of Physicists in Medicine guidelines in AAPM Task Group 101[21].

PD-1 inhibitor

All included patient patients were treated with PD-1 inhibitors within 7 days after the first TACE. PD-1 inhibitors included toripalimab (72.4%) and sintilimab (27.6%) (Supplementary Table 1).

Teriparatuzumab, 3mg/kg, by body weight, every 2 weeks; Sintilimab, 200 mg every three weeks. The specific doses and protocols used were strictly in accordance with the instructions for use. And the PD-1 inhibitors are all administered intravenously, into which low-grade infusion reactions occur, to reduce drip plasticity or suspend dosing, when symptoms resolve and resume medication and close observation. PD-1 inhibitors were continued until intolerable toxicity occurred.

Follow-up and assessment

All patients were followed up in the outpatient clinic every 1-3 months. At each follow-up visit, there were routine history taking physical examination, laboratory blood tests, and abdominal ultrasound or enhanced CT/MRI. The primary end point of this study was PFS, which was defined as the time from the first locoregional treatment after being diagnosed as PD-1 inhibitor-TACE refractory to tumor progression or death due to any cause. Assessment of tumor progression was based on the mRECIST. Overall survival (OS) was defined as the time from the first locoregional treatment after being diagnosed as PD-1 inhibitor-TACE refractory to death due to any cause or the recent follow-up.

Treatment-related adverse events (TRAEs) were obtained from clinic visit records or medical records and evaluated according to the criteria of the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). If multiple instances of the same toxicity occurred, the highest grade for each patient of a given category was adopted.

Statistical analysis

All clinical data were analyzed using IBM SPSS Statistics 23 or R 4.0 software (<http://www.r-project.org/>). The χ^2 test or Fisher exact test was used to compare variables. The Student's t-test was used to compare continuous variables and the χ^2 test or Fisher exact test was used to compare categorical variables. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratio (HR) was calculated by Cox regression models. And odd ratio (OR) was calculated by logistics regression models. $P < 0.05$ was defined as a significant difference.

Results

Patient characteristics and treatments

A Flow diagram for the present study is shown in Figure 1. Of 76 patients at the Eastern Hepatobiliary Surgery Hospital and the First Affiliated Hospital of Wenzhou Medical University with complete clinic and

follow-up data, 45 (59.2%) patients continued TACE combined with PD-1 inhibitor therapy and 31 (47.3%) switched SBRT combined with PD-1 inhibitor therapy. Table 1 summarizes the baseline features of these patients. There were no significant differences at baseline between the two groups, including age, gender, HBsAg, maximum tumor size, tumor number, alpha-fetoprotein concentration (AFP), Des-gamma-carboxy prothrombin (DCP), total bilirubin (TB), albumin, albumin-bilirubin grade, prothrombin time (PT), glucose, creatinine and Platelet.

Table 1
Baseline Characteristics of Study Patients

Characteristics	TACE (n=45)	SBRT (n=31)	P value
Age (year)			0.945
< 65	36 (86.2)	25 (78.8)	
≥ 65	9 (13.8)	6 (21.2)	
Gender			0.168
Female	6 (13.8)	8 (19.2)	
Male	39 (86.2)	23 (80.8)	
HBsAg			0.525
Positive	40 (82.8)	26 (78.9)	
Negative	5 (17.2)	5 (21.1)	
Maximum tumor size (cm)			0.275
< 5	28 (41.4)	23 (57.7)	
≥ 5	17 (58.6)	8 (42.3)	
Tumor number			0.137
2	31	20	
3	10	11	
4	4	0	
AFP (ng/mL)			0.610
< 400	22 (58.6)	17 (61.5)	
≥ 400	23 (41.4)	14 (38.5)	
DCP (mAU/mL)			0.555
< 2050	26 (65.5)	20 (73.1)	
≥ 2050	19 (34.5)	11 (26.9)	
TB (umol/L)			0.468
TACE, transcatheter arterial chemoembolization; AFP, alpha-fetoprotein concentration; DCP, Des-gamma-carboxy prothrombin; TB, total bilirubin; ALBI, albumin-bilirubin; PT, prothrombin time.			
Triple therapy, TACE combined with PD-1 inhibitor and anti-angiogenic therapy; Doublet therapy, TACE combined with PD-1 inhibitor therapy.			

Characteristics	TACE (n=45)	SBRT (n=31)	Pvalue
< 18.8	27	16	
≥ 18.1	18	15	
Albumin (g/L)			0.145
< 35	8	10	
≥ 35	37	21	
ALBI grade			0.243
1	25 (55.2)	13 (53.9)	
2	20 (41.4)	18 (46.1)	
3	0	0	
PT (sec)			0.669
< 13	36	26	
≥ 13	9	5	
Glucose (mmol/L)			0.337
< 7	39	29	
≥ 7	6	2	
Creatinine (umol/L, median)	66.0	61.0	0.222
Platelet (X10 ⁹ , median)	162.0	174.0	0.625
<i>TACE, transcatheter arterial chemoembolization; AFP, alpha-fetoprotein concentration; DCP, Des-gamma-carboxy prothrombin; TB, total bilirubin; ALBI, albumin-bilirubin; PT, prothrombin time.</i>			
<i>Triple therapy, TACE combined with PD-1 inhibitor and anti-angiogenic therapy; Doublet therapy, TACE combined with PD-1 inhibitor therapy.</i>			

The median follow-up for the entire cohort was 11.5 months. Of the 76 patients enrolled in the study, 41 patients died during the study (31 in the TACE group and 10 in the SBRT group), 24 were alive (8 in the TACE group and 16 in the SBRT group), and 11 were lost to follow-up (6 in the TACE group and 5 in the SBRT group).

Efficacy outcomes

The median PFS was 19.6 months (95% CI 13.1-26.1) in the SBRT group and 10.1 months (95% CI 7.3-12.9) in the TACE group. The median OS was 14.1 months in the TACE group and was not reached in the

SBRT group. The 1-year OS rate and PFS rate of SBRT group were 71.5% and 64.8%, respectively, while those of TACE group were 54.2% and 40.7%, respectively. SBRT significantly prolonged PFS relative to TACE (Figure 2A, HR=0.361, 95%CI 0.182-0.716, P < 0.05). Similarly, as shown in Figure 2B, SBRT significantly prolonged the OS of patients (HR=0.375, 95%CI 0.182-0.773, P < 0.05).

Table 2 summarizes the best tumor responses for the entire HCC patients. According to mRECIST 1.1, the ORR of 71.0% in the SBRT group was significantly higher than the 15.6% in the TACE group (OR=8.483, 95%CI 3.319-21.680, P < 0.001). And the disease control rate (DCR) of the SBRT group was also significantly higher than that of the TACE group (80.6% vs. 31.1%, OR=9.226, 95%CI 3.096-27.493, P < 0.001).

Table 2
Best tumor response

	TACE group (n=45)	SBRT group (n=31)	P value
CR	0	11(35.5)	
PR	7 (15.6)	11 (35.5)	
SD	7 (15.6)	3 (9.7)	
PD	31 (68.9)	6 (19.4)	
ORR	7 (15.6)	22 (71.0)	<0.001
DCR	14 (31.1)	25 (80.6)	<0.001
<i>TACE transcatheter arterial chemoembolization, SBRT stereotactic body radiation therapy, CR complete response, PR partial response, SD stable disease, PD progressive disease, ORR objective response rate, DCR disease control rate.</i>			

Safety outcomes

According to CTCAE version 5.0, TRAEs during treatment were evaluated according to frequency and severity. Almost all patients have transient TRAEs after receiving locoregional therapies and remit spontaneously within 24 to 48 hours. Therefore, we did not analyze and discuss these transient TRAEs.

As shown in Table 3, the most common TRAEs at all levels in the TACE group were decreased platelet count (44.4%), decreased albumin (37.8%), and elevated AST (37.8%). In addition, the most common grade 3/4 TRAEs was decreased platelet count (6.7%). In the SBRT group, the most common TRAEs were increased AST (51.6%), fatigue (48.4%) and decreased platelet count (48.4%), and the most common grade 3/4 TRAEs were lymphopenia (9.7%) and dysphagia (6.5%).

Table 3
Treatment emergent adverse events

Adverse Events	TACE (n=45)		SBRT (n=31)	
	Any grade, n (%)	Grade 3/4. n (%)	Any grade, n (%)	Grade 3/4. n (%)
Decreased albumin	17 (37.8)	0	13 (41.9)	0
Dysphagia	6 (13.3)	0	9 (29.0)	2 (6.5)
Decreased PLT	20 (44.4)	3 (6.7)	15 (48.4)	0
Elevated AST	17 (37.8)	2 (4.4)	16 (51.6)	2 (6.5)
Elevated ALT	13 (26.9)	2 (4.4)	14 (45.2)	2 (6.5)
Lymphopenia	0	0	5 (16.1)	3 (9.7)
Gastrointestinal hemorrhage	7 (15.6)	2 (4.4)	11 (35.5)	1 (3.2)
Dyspnoea	0	0	6 (19.4)	0
Radiation dermatitis	0	0	6 (19.4)	0
Cough	2 (4.4)	0	4 (12.9)	0
Elevated TB	10 (22.2)	0	8 (25.8)	0
Diarrhea	6 (13.3)	0	9 (29.0)	0
Fatigue	13 (28.9)	0	15 (48.4)	0
Hand-foot skin reaction	9 (20.0)	2 (4.4)	7 (22.6)	1 (3.2)
Elevated creatinine	2 (4.4)	0	2 (6.5)	0
Albuminuria/Proteinuria	2 (4.4)	0	1 (3.2)	0
Decreased appetite	4 (8.9)	0	4 (12.9)	0
Constipation	1 (2.2)	0	0	0
Infusion-related reaction	11 (24.4)	0	9 (29.0)	0
<i>TACE, transcatheter arterial chemoembolization; SBRT, stereotactic body radiation therapy; PLT, platelet; AST, aspartate transaminase; ALT, alanine aminotransferase; TB, total bilirubin.</i>				

Discussion

In this study, we report for the first time the efficacy of SBRT in patients with PD-1 inhibitor–TACE refractory intermediate-stage HCC. The results showed that switching to receive SBRT combined with PD-

1 inhibitors provided better long-term prognosis and tumor control than continued receive TACE combined with PD-1 inhibitors. This provides more options for the treatment of patients with BCLC stage B HCC.

TACE is the standard of care for patients with BCLC stage B HCC[6–9], but some patients develop TACE refractoriness and cannot achieve effective tumor control[10, 11]. Guidelines recommend that patients start receiving systemic therapy once they are diagnosed as TACE refractoriness[6, 8, 9]. Currently, the most commonly used drugs for systemic therapy include targeted anti-vascular agents such as sorafenib and lenvatinib. The results of several phase III trials suggest that TACE combined with sorafenib does not improve the long-term prognosis of patients[22–26], whereas the recent Japanese TACTICS trial demonstrated that sorafenib was able to prolong PFS of patients [27], while a large number of retrospective studies proved that the combination therapy of targeted anti-vascular agents and TACE was potentially beneficial for HCC patients[20, 28–32]. Although the efficacy of TACE combined with targeted anti-vascular agents is still controversial, the therapeutic modality of TACE combined with systemic therapy has exhibited its promise[33]. Meanwhile, PD-1 inhibitors have been increasingly investigated as representative agents for immunotherapy. And the possible mechanism of benefit of TACE combined with PD-1 inhibitor was uncovered: TACE could decrease the ratio of CD4⁺ / CD8⁺ cells and increase the level of PD-1 mRNA expression in patients with HCC[12]. Therefore, TACE combined with PD-1 inhibitor might have potential clinical value for patients with HCC. This was precisely verified by the recent report by Chen et al., in which patients had increased PD-1 inhibitor treatment on the basis of TACE with improved oncological outcomes[14]. However, the role of PD-1 inhibitors for patients is also limited[34], and once a patient presents refractory to both PD-1 inhibitors and TACE, what treatment should be followed up, which is a question worth exploring and urgently resolving.

Radiotherapy because the stronger hepatotoxicity limits its application, with the advancement of technology, SBRT is currently able to safely deliver high-dose radiotherapy to HCC, and the AASLD guidelines accepted SBRT as one of the treatments for HCC[7]. For patients with BCLC stage B HCC who received SBRT, the 2-year local control rate reached 61-81%[35]. Several retrospective controlled studies containing patients with intermediate stage HCC showed that SBRT had similar or even higher tumor control rates and OS than TACE[18, 19]. On the one hand, a clinical trial demonstrated the safety and feasibility of SBRT as a local salvage regimen for incomplete TACE[36]. Radiotherapy can trigger immunogenic cell death (ICD), resulting in the release of cytokines and damage associated molecular patterns (DAMPs). DAMPs can lead to the subsequent priming and trafficking of tumor specific T lymphocytes into the tumor microenvironment (TME) by enhancing the recruitment of antigen-presenting cells (APCs), the processing of tumor associated antigens (TAAs), and the cross presentation of antigenic peptides on major histocompatibility complex class I (MHC I), thereby enhancing the efficacy of PD-1 inhibitors[37]. And its clinical benefits have also been reported[36, 38, 39]. Therefore, we speculate that SBRT combined with PD-1 inhibitor may be a potential effective alternative treatment for patients who are refractory to PD-1 combined TACE.

Our results validate the above theory and suggest that this therapy of SBRT combined with PD-1 inhibitor can significantly improve the oncological outcomes of patients who are refractory to PD-1 inhibitor

combined with TACE. In this study that enrolled 76 patients proven to be refractory to PD-1 inhibitor TACE treatment, the SBRT group (n = 31) had a median PFS of 19.6 months (95% CI 13.1-26.1), which was significantly higher than the TACE group (n = 45) with a median PFS of 10.1 months (95% CI 7.3-12.9, $P < 0.001$). The 1-year OS rate and 1-year PFS rate in the SBRT group were 71.5% and 64.8%, and the ORR and DCR were 71.0% and 80.6%, respectively. The 1-year OS rate and 1-year PFS rate in the TACE group were 54.2% and 40.7%, and the ORR and DCR were 15.6% and 31.1%, respectively. Compared with TACE, SBRT significantly prolonged PFS (HR = 0.361, 95% CI 0.182-0.716, $P < 0.01$) and OS (HR = 0.375, 95% CI 0.182-0.773, $P < 0.001$), with better ORR (OR=8.483, 95%CI 3.319-21.680, $P < 0.001$) and DCR (OR = 9.226, 95% CI 3.096-27.493, $P < 0.001$) in PD-1 inhibitor–TACE refractory patients. In addition to efficacy, we analyzed TRAEs associated with SBRT plus PD-1 inhibitors. The most common TRAEs were increased AST (51.6%), fatigue (48.4%), and decreased platelet count (48.4%). The most common grade 3/4 TRAEs were lymphopenia (9.7%) and dysphagia (6.5%). This is close to previous reports[40], with no unexpected TRAEs present. Therefore, SBRT combined with PD-1 is an effective and safe treatment modality for patients with PD-1 inhibitor–TACE refractory intermediate-stage HCC.

This study has several limitations. First, this is a retrospective study with inherent defects. Second, the sample size included in this study was small with potential selection bias. Third, there was some heterogeneity in patient populations and treatment regimens, which may have affected our findings. A prospective study is therefore needed to confirm our conclusions.

In conclusion, switching to receive SBRT was effective as evidenced by an increase in PFS and OS in patients with PD-1 inhibitor–TACE refractory intermediate-stage HCC. To improve the survival of those patients, it is important to switch treatment from TACE to SBRT even if the tumor is still in the intermediate stage.

Declarations

Data Availability

Raw data can be provided on request by the Editor.

Author Contribution

Conception and Design: Shu-Qun Cheng, Yun-Feng Shan, Yan-Jun Xiang

Financial Support: Shu-Qun Cheng, Kang Wang, Yun-Feng Shan

Provision of Study Materials or Patients: Yun-Feng Shan, Kang Wang, Shuang Feng, Xi Cheng, Hong-Ming Yu, Xiao-Wei Li, Ying-Yi Qin, Li-Ping Zhou, Jian Zhai, Yan Meng

Collection and Assembly of Data: Yan-Jun Xiang, Kang Wang, Yi-Tao Zheng, Shuang Feng, Hong-Ming Yu, Yu-Qiang Cheng, Wei-Jun Wang

Data Analysis and Interpretation: Yan-Jun Xiang, Kang Wang, Yi-Tao Zheng, Shuang Feng, Ying-Yi Qin, Yun-Feng Shan, Shu-Qun Cheng

Manuscript Writing: All authors

Final Approval of Manuscript: All authors

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethics approval

This study was in compliance with the ethical standards of Declaration of Helsinki, and was approved by the Institutional Ethics Committees of the Eastern Hepatobiliary Surgery Hospital (EHBHKY2021-K-020) of the main center.

Consent to Participate

As patients' identities were anonymized, the requirement for informed consent was waived by the Ethics Committees.

Animal Research (Ethics)

Not applicable

Consent to Publish (Ethics)

Not applicable

Plant Reproducibility

Not applicable

Clinical Trials Registration

Not applicable

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Figures

Figure 1

Flow diagram for the present study BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; SBRT, stereotactic body radiation therapy.

Figure 2

Kaplan-Meier estimated PFS and OS curves in HCC patients with different therapies. (A) PFS; (B) OS. PFS, progression free survival; OS, overall survival; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; SBRT, stereotactic body radiation therapy.

Supplementary Files

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- [SupplementaryTable1.docx](#)