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High Dose-Volume SBRT Following TACE Improves Clinical Outcomes of Patients with Unresectable Hepatocellular Carcinoma

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Abstract

This study aimed to investigate the dose-volume effects of γ-ray stereotactic body radiotherapy (SBRT) on clinical outcomes of patients with huge-size (≥10 cm) unresectable hepatocellular carcinoma (HCC). A total of 59 patients with huge-size unresectable HCC were treated with SBRT following TACE between May 2006 and Dec. 2009. The analyzed parameters included fractional dose, marginal dose, maximal dose, and mean dose that the target received, as well as percentages of tumor volume encompassed by 60% (P_{60}), 70% (P_{70}), and 80% (P_{80}) of isodose curves in entire tumor. The clinical outcomes included objective response rate (ORR), disease-free survival (DFS), overall survival (OS), and adverse event (AE). During median follow-up of 18.4 months, 81.4% of ORR (8.5% CR and 72.9% PR) was achieved, higher than 28.9% of ORR recently reported for TACE alone. 1- and 3-year DFS rates were 31.1% and 2.6% with median DFS of 8.7 months; 1-, 3-, and 5-year OS rates were 46.5%, 13.7%, and 2.9%, with median OS of 11.8 months. P_{70} was the only factor significantly correlating to DFS (P = 0.009) and OS (P = 0.01). Neither severe radiation-related liver disease nor > grade 3 AE was observed. In conclusion, SBRT was a safe and effective option for treatment of huge-size unresectable HCC. P_{70} represented a parameter for predicting DFS and OS, and high dose-volume (e.g., P_{70}) might be required to achieve improved clinical outcomes of patients with this type of HCC.

Keywords

Stereotactic Body Radiotherapy, Dose-Volume Parameter, Disease-Free Survival, Overall Survival, Unresectable Hepatocellular Carcinoma

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, particularly in developing countries [1]. Recently, its incidence has been increasing in North America [2]. HCC is also the third leading cause of cancer-related deaths [3]. The 5-year overall survival rate of HCC is only 3% - 5% [4]. There are 10% - 20% of patients with newly diagnosed HCC that are larger than 10 cm in diameter [5]. To date, treatment option for huge-size (≥10 cm) HCC is very limited. PEI, RFA, and liver transplantation are usually not appropriate modalities for the treatment of patients with such large HCC [6]-[8]. Transarterial chemoembolization (TACE) alone is also unsatisfactory in treatment of large tumors [9]. Currently, hepatectomy is considered as the best option for the treatment of HCC [10]. However, a high recurrence rate (50% - 70%) remains a major issue after curative tumor resection [11] [12]. Furthermore, many cases of huge-size HCC are unresectable [13] [14]. Therefore, effective treatments for such a type of HCC are desperately needed.

In earlier radiotherapy, the whole liver was irradiated to treat HCC. The dose for the whole-liver radiotherapy that could be tolerated was too low to affect tumor [15]-[17]. As consequence, radiotherapy had not been widely used in the management of patients with HCC. With the recent advances in science and technology, radiotherapy had emerged as a potentially curative option in the treatment of HCC [18]. Among many others, stereotactic body radiotherapy (SBRT, also known as hypo-fractionated radiotherapy) represented one of the most advanced technologies in radiotherapy. Several studies had demonstrated that SBRT had the significant therapeutic effects on HCC [19]-[25]. In this context, a phase 2 trial was currently ongoing to evaluate the effectiveness and adverse event of SBRT in the patients with unresectable HCC who had solitary 3 cm or less size HCC without extrahepatic lesion and vascular involvement (https://clinicaltrials.gov/ct2/show/NCT01910909). Moreover, since August 2014, Radiation Therapy Oncology Group (RTOG) has been conducting a phase 3 randomized multicenter trial (RTOG 1112) to determine if SBRT followed by Sorafenib improve overall survival in unresectable HCC patients, by comparing to Sorafenib alone (https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1112). However, there were few reports on the role of SBRT in the treatment of huge-size HCC. Furthermore, as the dose-volume parameters of SBRT were entirely different from those of the conventional radiotherapy, it remained virtually unknown whether dose-volume parameters would impact on patient outcomes when SBRT was used to treat huge-size HCC. To this end, the present study was designed to investigate the effect of SBRT with high dose-volume parameters after incomplete TACE on the clinical outcomes of patients with huge-size unresectable HCC.

2. Materials and Methods

2.1. Patient Eligibility

This study was approved by the Ethics Committee of the Fuzhou General Hospital, and performed according to the Declaration of Helsinki. Written informed consent was obtained from each patient before treatment with TACE and SBRT. A total of 716 consecutive HCC patients were routinely treated with γ-ray SBRT as standard care between May 2006 and Dec. 2009 at the Tumor Radiotherapy Center, Fuzhou General Hospital, China. Among them, 59 patients were eligible for this study. The criteria for patients to be enrolled include: 1) unresectable HCC; 2) tumor size ≥ 10 cm in diameter; 3) Child-Pugh Class, A or B; 4) Eastern Cooperative Oncology Group Performance Status (ECOG PS), 0 - 2; 5) no extrahepatic metastasis; 6) SBRT post incomplete TACE for treatment; and 7) no history of liver radiotherapy. All patients had contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET) of abdomen. HCC was diagnosed by cytological/histological evidence (n = 51); one radiological image showing characteristic features of HCC, together with an elevated AFP level (>400 ng/ml, n = 3); or at least two radiological images showing characteristic features of HCC (n = 5). 59 patients were divided into group A ($P_{70} \geq 60\%$, n = 27) and B ($P_{70} < 60\%$, n = 32). Characteristics of the patients were summarized in **Table 1**.

2.2. Treatment

TACE was carried out by infusion with the mixture of 5 - 10 ml iodized oil (Lipiodol; Guerbet, Charles de Gaulle, France) and 1 mg/kg cisplatin (Dong-A Pharm. Co. Ltd., Seoul, Korea), followed by gelatin sponge cubes (Gelfoam; Upjohn, Kalamazoo, MI). Tumor feeding arteries were carefully selected for TACE, in order to preserve liver function the best. When there was an arterio-portal shunt, TACE was performed without Lipiodol

Table 1. Characteristics of the patients (n = 59).

Characteristic	Group A		Group B	
	Value	No. of patient (%)	Value	No. of patient (%)
Age, year				
Range	41 - 65		38 - 64	
Mean	53		51	
Gender				
Male		22 (81.5)		26 (81.3)
Female		5 (18.5)		6 (18.7)
ECOG PS				
0		2 (7.4)		3 (9.4)
1		20 (74.1)		23 (71.9)
2		5 (18.5)		6 (18.7)
Child-Pugh				
A		20 (74.1)		24 (75)
B		7 (25.9)		8 (25)
AFP (ng/mL)				
≥400		22 (81.5)		25 (78.1)
<400		5 (18.5)		7 (21.9)
HBsAg positive		21 (77.8)		23 (71.9)
Anti-HCV positive		3 (11.1)		4 (12.5)
C/h confirmation				
Yes		24 (88.9)		27 (84.4)
No		3 (11.1)		5 (15.6)

ECOG PS, Eastern Cooperative Oncology Group performance status; C/h, cytological/histological; AFP, alpha-fetoprotein; HBsAg, hepatitis B surface antigen.

to prevent severe damage of normal liver tissue.

SBRT was administrated using the total body γ-ray stereotactic radiotherapy system (OUR company, Shenzhen, China) 2 - 4 weeks after TACE. Briefly, patients were immobilized by vacuum cushions and underwent CT scan in supine or prostrate position. The CT data were then transferred to the SBRT Treatment Planning System (SGI, Southeast University, China). Body surface, tumor contour, and some important normal tissues were reconstructed to display three-dimensional (3D) representation based on cross-sectional imaging. Clinical target volume (CTV) is defined as the macroscopic volume of tumor. The planning target volume (PTV) was created by asymmetrically expanding the CTV by 0.5 - 1.0 cm. The position, number, and size of focused fields were carefully selected to enhance the dose for PTV but minimize both the dose for normal tissues and irradiated tissue volumes. The dose-volume histogram (DVH) generated was then used to evaluate the treatment planning. Dose prescription was normalized at the 50% or 55% isodose curves encompassing 100% of PTV. Images were taken to verify the tumor localization and patient position before SBRT. Marginal dose and fractional dose determined dependently upon predicted toxicity of normal tissues and the function of reserved liver tissue. The marginal dose of 37.6 ± 2.9 Gy was delivered in 12 - 14 days with fractional dose of 2.8 ± 0.2 Gy and 6 fractions per week. All patients had one day of rest after every 6 consecutive fractions of treatment. The dose-volume parameters of tumors were shown in **Table 2**.

2.3. Evaluation of Clinical Outcomes

Complete blood counts (CBC) and liver function were assessed weekly during treatment. Tumor size within the

Table 2. Dose-volume parameters.

Variable	Group A	Group B
PTV (cc)		
Range	283 - 818	292 - 823
Median	574	581
Delivered dose dose (Gy)		
Marginal	35.2 - 40.4	34.7 - 40.5
Maximal	61.8 - 67.1	59.7 - 68.5
Mean	48.2 - 51.8	46.2 - 53.4
Fractional	2.6 - 3.0	2.6 - 3.0
Dose-volume, %		
P_{50}	100	100
P_{60}	76 - 95	67 - 89
P_{70}	60 - 72	38 - 58
P_{80}	25 - 42	15 - 34

radiated field was measured based on CT and/or MRI scan 4 weeks after treatment completed followed by once for every 1 to 3 months afterwards. According to the Response Evaluation Criteria in Solid Tumors (RECIST), complete response (CR) was defined as disappearance of tumor, partial response (PR) as a >30% decrease in tumor size, progressive disease (PD) as >20% in-field tumor growth or new tumor appearance, and stable disease (SD) as neither PR nor PD criteria met. Objective response rate (ORR) was defined as a sum of CR and PR. Survival time was defined as a period from the date to start treatment to the date of death or for the last follow-up.

Acute and later toxicities were assessed using the National Cancer Institute (NCI) Common Toxicity Criteria Version 2.0 and the Late Radiation Morbidity Scoring Scheme of Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC), respectively.

2.4. Statistical Analysis

Kaplan-Meier method was used to analyze overall survival (OS) rate. Survival curves were compared using the log-rank test. For multivariate analysis to evaluate the relation between the OS and various parameters, the stepwise procedure was performed using the Cox regression model. $P < 0.05$ was considered as statistically significant. All statistical analyses were conducted using the SPSS 16.0 (SPSS, Chicago, IL, USA) statistical software package.

3. Results

3.1. Tumor Response

Among 59 patients, 5 (8.5%) and 43 (72.9%) achieved CR and PR, respectively, yielding 81.4% of ORR. In addition, 7 (11.9%) patients had SD, while 4 (6.7%) patients experienced PD. The median follow-up time was 18.4 months. Representative CT images before and after SBRT were shown in a patient who achieved a CR (**Figure 1**), in whom no tumor recurrence within the irradiated field was observed in 63 months after SBRT. Tumor responses are then compared between group A ($P_{70} \geq 60\%$) and B ($P_{70} < 60\%$). As shown in **Table 3**, 4 patients in group A achieved CR, while only one with a CR in group B. However, the number of patients with PR as well as ORR were similar between these two groups. These findings argue that SBRT following incomplete TACE is effective in the treatment of patients with huge-size unresectable HCC. They also raise a possibility that although there is no significant difference in ORR, $P_{70} \geq 60\%$ might yield higher CR than $P_{70} < 60\%$.

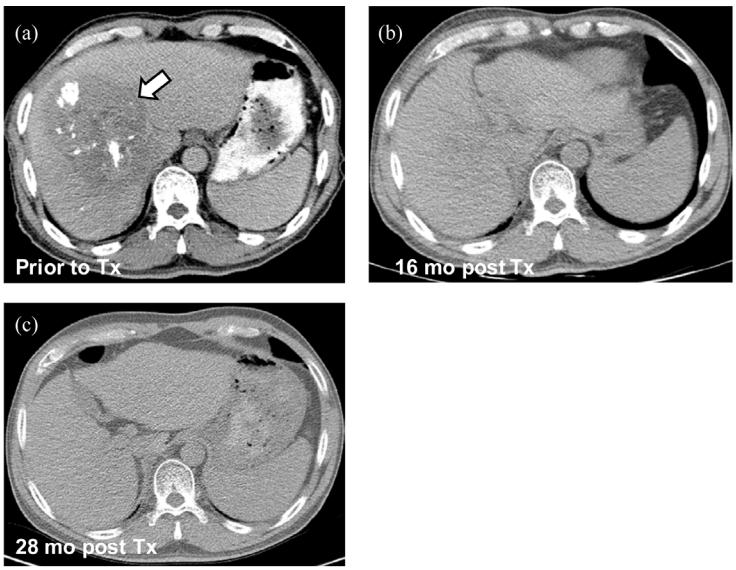

Figure 1. Representative images of abdominal CT scan in a male patient with huge-size HCC who achieved a CR after treated (Tx) with SBRT (3.0Gy/F × 13F/2w) following TACE. The images were captured before SBRT (a), 16 months (mo, b), and 28 months after SBRT (c), respectively. Arrow indicates the huge-size HCC tumor.

Table 3. Tumor response after treated with SBRT following TACE.

Response	No. of patient (%)		
	Group A	Group B	Total
Complete response (CR)	4 (14.8)	1 (3.1)	5 (8.5)
Partial response (PR)	21 (77.8)	22 (68.8)	43 (72.9)
Stable disease (SD)	1 (3.7)	6 (18.7)	7 (11.9)
Progressive disease (PD)	1 (3.7)	3 (9.4)	4 (6.7)
Objective response (OR = CR + PR)	25 (92.6)	23 (71.9)	48 (81.4)

3.2. Survival

All of 59 patients were followed up for 4 to 70 months (median 18.4 months). Kaplan-Meier analysis revealed that 1- and 3-year DFS rates were 31.1% and 2.6%; 1-, 3-, and 5-year OS rates were 46.5%, 13.7%, and 2.9%; median DFS (**Figure 2(a)**) and OS (**Figure 2(b)**) were 8.7 and 11.8 months, respectively. Cox regression multivariate analysis demonstrated that while marginal dose, maximal dose, mean dose, and P60 were not related with either DFS or OS, P70, P80, fractional dose, and Child-Pugh class (A versus B) were likely associated with DFS and OS. However, the likelihood of P80 (P = 0.054 for DFS and 0.063 for OS), fractional dose (P = 0.071 for DFS and 0.076 for OS), and Child-Pugh class (P = 0.066 for DFS and 0.068 for OS) were not statistically significant. Of note, P70 was the only factor significantly predicting both DFS (P = 0.009) and OS (P = 0.01). 1- (51.6%) and 3-year (5.4%) DFS rates in group A ($P_{70} \geq 60\%$) were higher than those (10.1% and 0%, respectively) in group B ($P_{70} < 60\%$). Consistently, 1- (69.7%), 3- (23.6%), and 5-year (6.1%) OS rates in group A were also higher than those (23.2%, 4.2%, and 0%, respectively) in group B. Median DFS (**Figure 2(c)**), and OS (**Figure 2(d)**) were 11.6 and 18.3 months for group A versus 7.1 and 9.6 months for group B. The findings indicate that SBRT following incomplete TACE improve survival of patients with huge-size unresectable HCC, and that the dose-volume parameter $P_{70} \geq 60\%$ is significantly better than $P_{70} < 60\%$.

3.3. Safety

All of 59 patients completed the treatment with γ-ray SBRT following incomplete TACE. The maximal doses

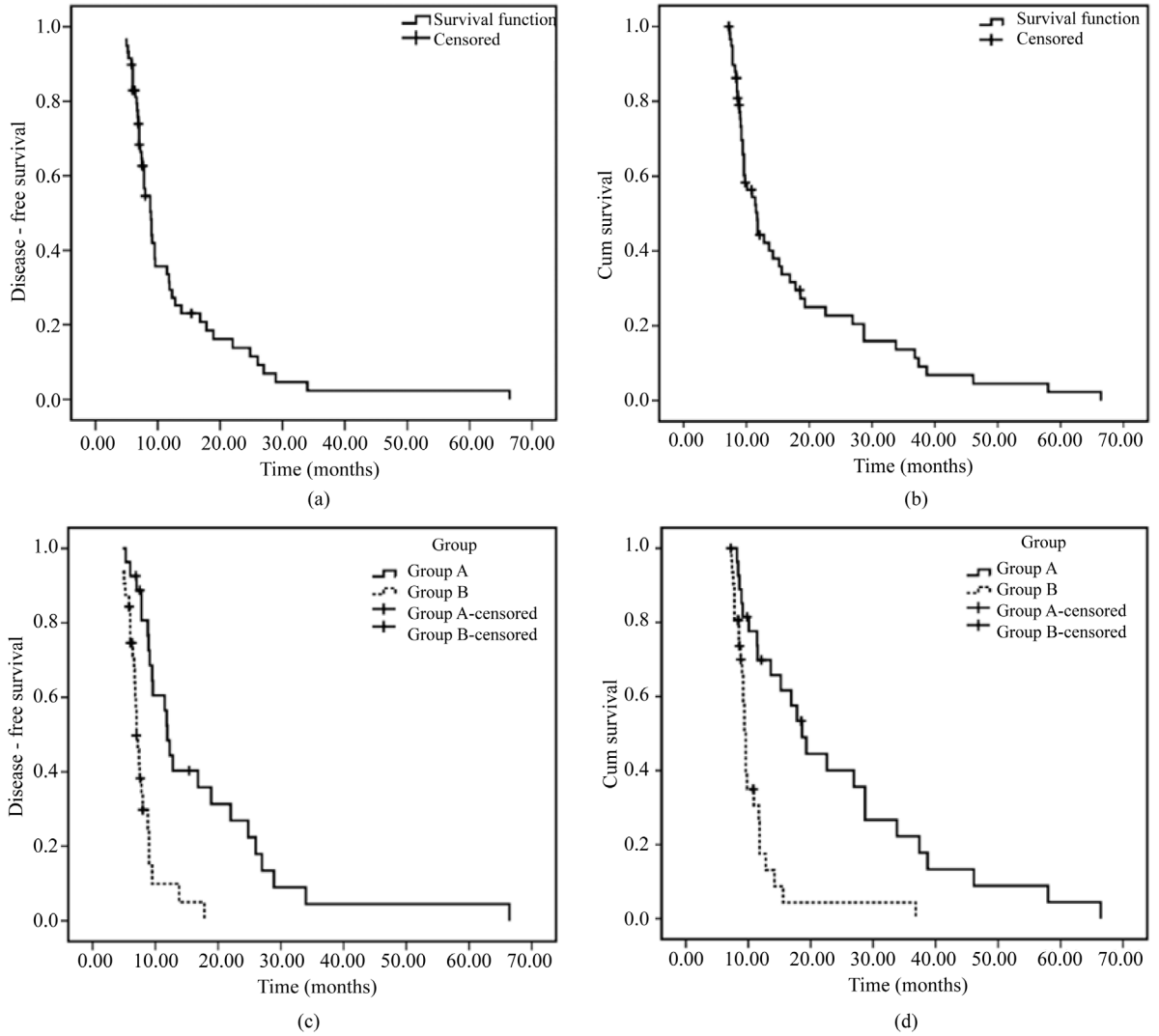

Figure 2. (a-b) Kaplan-Meier analysis of disease-free survival (DFS, a) and overall survival (OS, b) in all patients (n = 59) with huge-size HCC who received SBRT following TACE. (c-d) Multivariate analysis of DFS (c) and OS (d) between group A (70% isodose curve encompassing ≥ 60% of entire tumor) vs. group B (70% isodose curve encompassing < 60% of entire tumor).

that normal tissues were irradiated were shown in **Table 4**. The complications and toxicities of the patients were shown in **Table 5**. No severe radiation-induced liver disease (RILD) observed during the median follow-up period of 18.4 months (range, 4 - 70 months). Grade 1 - 2 of liver and gastrointestinal AE were observed in 3 (5.1%) and 5 (8.5%) of 59 patients, respectively, while no > grade 3 AE was observed. Fatigue was the major complication observed in 40.7% (24/59) patients. The symptoms of these patients either disappeared spontaneously or were manageable. The dermatitis represented another common complication, and 2 (3.4%) of 59 patients experienced grade 3 dermatitis that was difficult to be managed. It is noteworthy that both these two patients had extremely large tumors (*i.e.*, 16.8 cm and 17.6 cm, respectively). that were therefore very close to skin. Thus, these findings indicate that γ-ray SBRT following incomplete TACE is safe in the treatment of patients with huge-size unresectable HCC.

4. Discussion

Currently, treatment options for huge-size (≥10 cm in diameter) HCC are limited. Disease with large tumor is most likely to recur after treatment [26]-[28], probably due to unrecognized small-vessel tumor invasion [29].

Table 4. Maximal doses that normal tissue is irradiated.

Dose (Gy)	Group A			Group B		
	s.c. tissue	Stomach	Duodenum	s.c. tissue	Stomach	Duodenum
Fractional dose (max)	3.0	2.3	2.1	3.0	2.5	2.3
Total dose (max)	42	32	27.2	42	32.5	29.9

s.c., subcutaneous; max, maximum.

Table 5. SBRT-related adverse events (AEs).

AE	Group A, no. of patient (%)			Group B, no. of patient (%)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Edema	1 (3.7)	0	0	1 (3.1)	0	0
Anemia	1 (3.7)	0	0	0	0	0
GI	1 (3.7)	1 (3.7)	0	2 (6.2)	1 (3.1)	0
Fatigue	6 (22.2)	4 (14.8)	0	9 (28.1)	5 (15.6)	0
Nausea	2 (7.4)	1(3.7)	0	3 (9.4)	2 (6.3)	0
Dermatitis	2 (7.4)	5 (18.5)	1 (3.7)	3 (9.4)	8 (25)	1 (3.1)
Liver function	1 (3.7)	0	0	1 (3.1)	1 (3.1)	0

GI, gastrointestinal.

Large tumor usually portends an unfavorable factor for patient prognosis [30]. Among others, the recently advanced radiotherapy represents a promising option for the treatment of patients with large-size HCC. In this context, our previous work has demonstrated the rationale for combining SBRT and TACE in treatment of HCC [21]. However, it remains unclear whether this combination radiotherapy could also benefit patients with large HCC tumors. To this end, clinical outcomes of 59 patients with huge-size unresectable HCC who had received SBRT following incomplete TACE were analyzed in the present study. Notably, after treated with this combination radiotherapy, 81.4% of patients with huge-size unresectable HCC achieved objective tumor responses, including 8.5% CR and 72.9% PR, while the ORR was much higher than those (29%, including 4.3% CD and 24.6% PR) reported very recently for TACE alone in treatment of huge-size HCC [31].

Of note, the dose prescription used in this study was different from other SBRT approaches for treatment of HCC [32]. The doses at 50% or 55% isodose curve by which the entire PTV was encompassed were normalized, while the higher isodose curves (e.g., 60%, 70%, and 80%) were all remained in the GTV. In addition, the range of P_{70} was 38% - 72%. These modifications yielded a much higher dose in GTV than in normal tissue around the tumor. Therefore, the high-dose in GTV is most likely responsible for the high ORR observed in this study such a high ORR.

It has been reported the survival rates of HCC patients treated with SBRT are similar to those treated with charged particle therapy [33]. The present study provide first evidence that the modality combining SBRT with TACE markedly prolonged overall survival of patients with large tumor HCC, with median OS of 11.8 months that almost doubled when compared to TACE alone (median OS = 6.5 months) [31]. Moreover, the present results also raise a notion that the higher dose-volume might be more beneficial to patient survival. Multivariate analysis indicated that while P_{70}, P_{80}, fractional dose, and Child-Pugh class were associated with DFS and OS, P_{70} is the only one statistically significant factors to predict patient survival. To this context, $P_{70} \geq 60\%$ yielded 1-, 3-, 5-year OS rates as 69.7%, 23.6%, and 6.1%, respectively, with the median OS of 18.3 months, comparable to those (37.8%, 16.3%, and 9.7%) reported recently for TACE alone [34]. Consistent with the results that a higher ORR was achieved with larger P_{70}, the difference in patient survival between two levels of dose-volume parameters (*i.e.*, $P_{70} \geq 60\%$ versus $P_{70} < 60\%$) indicates that the high dose-volume (for P_{70} in particular) played an important role in outcomes of patients with huge-size unresectable HCC after received SBRT.

Both severe gastrointestinal AE and radiation-induced liver disease (RILD) have been reported after treatment of HCC with volumetric modulated arc therapy [35]. In contrast, neither severe (grade ≥ 3) RILD nor gastrointestinal AE was observed in the present study. The major toxicities included fatigue and grade 1 - 2 dermatitis, while grade 3 dermatitis was seen only in 3.4% (2/59) patients at 3 - 4 months after treatment with SBRT. It is noteworthy that both of these two patients who experienced grade 3 dermatitis had extremely large tumors that were >16 cm in diameter, as well as very close to skin. In the present study, all patients received daily fraction of 2.6 - 3.0 Gy with 6 fractions per week for 12 - 14 days, these fractional doses are higher than the conventional radiotherapy. Thus, severe dermatitis might be related to the high dose radiation, which it raises a possibility that dose or time of SBRT might need to be optimized to avoid such a severe adverse event (AE) in treatment of very large HCC tumor (e.g., >16 cm), particularly when tumor is near skin. In this context, it has been suggested that administration of radiotherapy for a shorter period of time might be more appropriate for treatment of HCC patients [36]. Nevertheless, although it is rare, severe dermatitis should be taken into consideration to treat extremely large HCC tumors with high dose-volume SBRT.

5. Conclusion

Together, these results suggest that the modality combining SBRT and TACE is a safe and effective in the treatment of patients with huge-size unresectable HCC. It is noteworthy that among several key factors tested, the dose-volume P_{70} is the only one parameter that is able to statistically significantly predict better survival (e.g., longer DFS and OS) in this population of patients who receive SBRT and TACE in combination. Therefore, high dose-volume (e.g., $P_{70} \geq 60\%$) plays an important role in efficacy of this regimen. However, there are certain limitations in this study due to the nature of a retrospective study. In addition, the percentage of tumor volume in entire liver is not taken into account in this study. Therefore, although future perspective randomized studies are required to define efficacy and safety of SBRT combined with TACE, the promising patient outcomes observed in this study argue strongly that this combination radiotherapy warrants further attention in the treatment of patients with huge-size unresectable HCC.

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