

Efficacy of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis/inferior vena cava tumor thrombosis: evaluation by comparison with conventional three-dimensional conformal radiotherapy

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ABSTRACT

This study aimed to evaluate the efficacy of stereotactic body radiotherapy (SBRT) compared with three-dimensional conformal radiotherapy (3DCRT). Forty-three patients with portal vein tumor thrombosis (PVTT)/inferior vena cava tumor thrombosis (IVCTT) treated with SBRT (27 with CyberKnife (CK) and 16 with TrueBeam (TB)) from April 2013 to December 2014, and 54 treated with 3DCRT from June 2008 to March 2013 were evaluated. Dosimetric parameters, response to radiotherapy (RT) and survival outcomes were compared in total SBRT vs. 3DCRT, CK vs. 3DCRT and TB vs. 3DCRT, respectively. The median biologically effective dose 10 (BED₁₀) values in total SBRT, CK, TB and 3DCRT were 73.4 Gy₁₀, 75.0 Gy₁₀, 60.5 Gy₁₀ and 58.5 Gy₁₀, respectively ($P < 0.001$ in total SBRT vs. 3DCRT, $P < 0.001$ in CK vs. 3DCRT, $P = 0.004$ in TB vs. 3DCRT). The tumor response rates were 67%, 70%, 62% and 46%, respectively ($P = 0.04$, $P = 0.04$, $P = 0.25$). The 1-year overall survival rates were 49.3%, 56.7%, 38.1% and 29.3%, respectively ($P = 0.02$, $P = 0.02$, $P = 0.30$), and the 1-year local progression rates were 20.4%, 21.9%, 18.8% and 43.6%, respectively ($P = 0.01$, $P = 0.04$, $P = 0.10$). The use of SBRT made it possible to achieve a higher BED₁₀ compared with the use of 3DCRT. Improvements in local control and survival were achieved in the CK group and the total SBRT group. Our results suggest that SBRT may have the potential to be the standard RT technique for the treatment of PVTT/IVCTT.

KEYWORDS: portal vein tumor thrombosis, inferior vena cava tumor thrombosis, hepatocellular carcinoma, stereotactic body radiotherapy, three-dimensional conformal radiotherapy

INTRODUCTION

Vascular invasion, such as portal vein tumor thrombosis (PVTT) or inferior vena cava tumor thrombosis (IVCTT), is a common condition in advanced hepatocellular carcinoma (HCC), with an incidence of 12.5 to 39.7% at the time of diagnosis [1]. PVTT/IVCTT sometimes causes deteriorative and aggressive features such as intrahepatic tumor dissemination, portal vein hypertension and ischemic liver damage, which lead to severe liver insufficiency. HCC patients with PVTT/IVCTT have an extremely poor prognosis; untreated patients have median survival times of 2 to 4 months [2]. Most patients with PVTT/IVCTT are unsuitable for surgery, and the efficacy of transarterial chemoembolization (TACE) is limited, with a 1-year overall survival time of 22.0 to 30.9% [3–5]. Therefore, treatment of HCC complicated by PVTT/IVCTT has always been challenging.

Regarding the role of radiotherapy (RT), the effectiveness of three-dimensional conformal radiotherapy (3DCRT) has been recognized for treating PVTT/IVCTT [6–10]. In addition to using 3DCRT alone [6–8], its combination with other local modalities such as TACE or transcatheter arterial infusion (TAI) has been recognized to be effective [9, 10]. Furthermore, a higher RT dose has been shown to improve both tumor response rate and overall survival (OS) in several retrospective 3DCRT studies, where the response rates in the high dose group (defined as those prescribed the biologically effective dose 10 (BED_{10}) ≥ 58 Gy₁₀) and the low dose group (defined as those prescribed $BED_{10} < 58$ Gy₁₀) were 54.6 to 80.0% and 20.0 to 21.7%, respectively, and OS rates in each group were 59.3% and 29.2%, respectively [7, 8]. Thus, delivering a higher dose to treat PVTT/IVCTT has become an important issue.

Development in RT techniques is remarkable, and one of the newest high-precision techniques is stereotactic body radiotherapy (SBRT), which allows for the delivery of higher doses accurately to the tumor, usually with hypofractionation. SBRT has been widely introduced and mainly used for treating lung tumors. In recent years, several reports on the effectiveness and safety of SBRT for treating HCC have been published [11–13]. Considering the results of these reports, use of SBRT to target PVTT/IVCTT may also have the potential to improve the survival outcomes of patients with HCC by controlling the progression of PVTT/IVCTT. However, at present, only a few studies have been reported investigating the efficacy of SBRT for treating PVTT/IVCTT [14–16]. Moreover, only one prospective study attempted to compare the results of treating PVTT/IVCTT with SBRT or 3DCRT. However, that study could not prove the advantages of SBRT in either tumor control or survival because far fewer patients were evaluable than expected [16].

The purpose of this study was to clarify the efficacy of SBRT for PVTT/IVCTT as compared with conventional 3DCRT. Dosimetric analyses regarding BED_{10} dosages to the target and dose–volume histogram (DVH) parameters including the organs at risk (OAR) were performed. Tumor response and survival data were also analyzed and compared.

MATERIALS AND METHODS

Patients

In April 2013, SBRT was initiated for the patients with PVTT/IVCTT from HCC and it was determined as the primary RT technique at our institutions. Since then, 43 consecutive patients with

PVTT/IVCTT have been treated with SBRT up until December 2014, and all of them were included in this study. Of these 43 patients, 27 were treated by using CyberKnife (CK) (Accuray Inc., Sunnyvale, CA, USA), and 16 by using TrueBeam (TB) (Varian Medical System, Palo Alto, CA, USA). Before April 2013, from June 2008 to March 2013, all patients were treated with 3DCRT. Although it was suspended after the initiation of SBRT, 54 consecutive patients were treated with 3DCRT during that time period, and all of them were included in this study for comparison with SBRT. In total, 97 patients with PVTT/IVCTT were retrospectively evaluated.

The diagnosis of HCC was made based on the American Association for the Study of Liver Disease (AASLD) guidelines [17]. Portal vein or inferior vena cava invasion was identified by the presence of a low-attenuation intraluminal filling defect adjacent to the primary tumor on contrast-enhanced computed tomography (CT). Basic indications for RT for PVTT/IVCTT were determined as follows: (1) tumor thrombus involving the main trunk and/or branches of the portal vein or those involving the inferior vena cava; (2) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 [18]; (3) no refractory ascites; (4) Child–Pugh classification A and B; and (5) no previous RT to the liver. All of the patients fulfilled these indications, including a few exceptions who were considered as suitable for RT; four Child–Pugh classification C patients who had a good PS of 0–1 and three patients who had Child–Pugh classification B with a PS of 3 were included because control of their tumor thrombosis was expected to improve their survival.

Most of the 97 patients had a history of previous treatment for intrahepatic disease. In particular, tumor resection was performed for 1 (4%), 3 (19%) and 6 (11%) patients treated with CK, TB and 3DCRT, respectively. TACE was performed for 15 (56%), 10 (63%) and 24 (44%) patients, respectively. Both tumor resection and TACE were performed for 7 (26%), 0 (0%) and 12 (23%) patients, respectively. Other treatments were administered for 3 (11%), 2 (13%) and 1 (2%) patients, respectively. In total, 26 of 27 patients (96%) treated with CK, 15 of 16 (94%) patients treated with TB and 43 of 54 (80%) patients treated with 3DCRT received previous treatment for intrahepatic lesions. Regarding post-treatment, to the best of our knowledge, sorafenib was used in 3 patients in the CK group, 3 patients in the TB group and 13 patients in the 3DCRT group. Written informed consent was obtained from all patients. This study was approved by the institutional review board of Kobe University Hospital and Kobe Minimally Invasive Cancer Center, and was conducted in accordance with the principles of the Declaration of Helsinki.

Radiotherapy

RT was performed primarily to treat PVTT or IVCTT. Any remaining tumors and other intrahepatic tumors were usually treated with TACE or TAI a few weeks before or after RT as a combined therapy. The cases treated with TAI during RT were not included in this study. In cases where TACE or TAI were difficult to perform because of huge or multiple tumors with severe liver dysfunction, RT for PVTT or IVCTT was administered as the sole treatment. Details of combined treatment are shown in Table 1.

SBRT was performed using CK or TB. For the SBRT planning, during the simulation the patients were placed in the supine position with both arms raised above the head with immobilization by vacuum pillow. Contrast-enhanced four-dimensional CT (4DCT) was

Table 1. Comparison of baseline characteristics between the patients treated with CK, TB and 3DCRT

Characteristics	SBRT		3DCRT (n = 54)	P value	
	CK (n = 27)	TB (n = 16)		CK vs. 3DCRT	TB vs. 3DCRT
Age (years)					
<70	11 (40%)	8 (50%)	30 (56%)	0.21	0.70
≥70	16 (59%)	8 (50%)	24 (44%)		
Median (range)	72 (52–88)	68.5 (44–86)	69 (38–83)		
Gender					
Male	24 (89%)	12 (75%)	49 (91%)	1	0.19
Female	3 (11%)	4 (25%)	5 (9%)		
ECOG performance status					
0–1	25 (93%)	13 (81%)	45 (83%)	0.41	1
2–3	2 (7%)	3 (19%)	9 (17%)		
Liver disease					
Hepatitis B	4 (15%)	4 (25%)	12 (22%)	0.67	0.91
Hepatitis C	16 (59%)	7 (44%)	27 (50%)		
Other	7 (26%)	5 (31%)	15 (28%)		
Child–Pugh classification					
A	14 (52%)	8 (50%)	27 (50%)	1	0.90
B	12 (44%)	7 (44%)	25 (46%)		
C	1 (4%)	1 (6%)	2 (4%)		
Albumin (g/dl)					
>3.5	9 (33%)	7 (44%)	13 (24%)	0.08	0.38
≥2.8 and ≤3.5	16 (59%)	6 (37%)	25 (46%)		
<2.8	2 (8%)	3 (19%)	16 (30%)		
Median (range)	3.3 (2.4–4.4)	3.5 (2.0–4.2)	3.1 (2.1–4.7)		
Total bilirubin (mg/dl)					
>3.0	0 (0%)	1 (6%)	1 (2%)	0.70	0.49
≥2.0 and ≤3.0	0 (0%)	0 (0%)	3 (6%)		
<2.0	27 (100%)	15 (94%)	50 (92%)		
Median (range)	0.8 (0.3–1.7)	0.9 (0.3–13.9)	1.0 (0.3–8.0)		
Prothrombin time (%)					
>70	16 (59%)	11 (69%)	45 (83%)	0.02	0.35
≥40 and ≤70	11 (41%)	5 (31%)	8 (15%)		
<40	0 (0%)	0 (0%)	1 (2%)		
Median (range)	72.2 (48.5–105.1)	77.3 (45.8–105.0)	79.6 (23.4–121.0)		

Continued

Table 1. Continued

Characteristics	SBRT		3DCRT (<i>n</i> = 54)	P value	
	CK (<i>n</i> = 27)	TB (<i>n</i> = 16)		CK vs. 3DCRT	TB vs. 3DCRT
Platelet count (0.000/mm ³)					
>100	14 (52%)	10 (63%)	35 (65%)	0.54	0.79
≥50 and ≤100	11 (41%)	6 (37%)	16 (29%)		
<50	2 (7%)	0%	3 (6%)		
Median (range)	10.4 (3.1–20.2)	11.7 (6.5–19.7)	12.5 (2.6–33.5)		
AFP (ng/ml)					
<400	19 (70%)	11 (69%)	28 (52%)	0.17	0.43
≥400	8 (30%)	5 (31%)	26 (48%)		
Median (range)	46 (1.3–357 250)	19 (2.6–134 060)	374 (2–62 969)		
PIVKA-II (mAU/ml)					
<400	10 (37%)	6 (37%)	19 (35%)	0.87	0.87
≥400	17 (63%)	10 (63%)	35 (65%)		
Median (range)	1097 (9–53 915)	1157 (31–69 126)	1716 (9–505 610)		
Thrombus location					
PV branchus	15 (46%)	5 (31%)	33 (61%)	0.59	0.11
PV trunk	10 (37%)	7 (44%)	14 (26%)		
IVC	2 (7%)	3 (19%)	4 (7%)		
IVC + PV	0 (0%)	1 (6%)	3 (6%)		
TNM stage					
II	6 (22%)	1 (6%)	8 (15%)	0.82	0.84
IIIa	0 (0%)	0 (0%)	1 (2%)		
IIIb	19 (71%)	13 (81%)	38 (70%)		
IVb	2 (7%)	2 (13%)	7 (13%)		
LN metastases					
Absent	27 (100%)	15 (94%)	53 (98%)	1	0.41
Present	0 (0%)	1 (6%)	1 (2%)		
Distant metastases					
Absent	25 (93%)	14 (87%)	47 (87%)	0.71	1
Present	2 (7%)	2 (13%)	7 (13%)		
Previous treatment to intrahepatic lesions					
Yes	26 (96%)	15 (94%)	43 (80%)	0.053	0.27
No	1 (4%)	1 (6%)	11 (20%)		

Continued

Table 1. Continued

Characteristics	SBRT		3DCRT (<i>n</i> = 54)	P value	
	CK (<i>n</i> = 27)	TB (<i>n</i> = 16)		CK vs. 3DCRT	TB vs. 3DCRT
Combined treatment					
TACE	9 (33%)	2 (13%)	19 (35%)	0.18	0.06
TAI	6 (22%)	5 (31%)	21 (39%)		
No	12 (45%)	9 (56%)	14 (26%)		

AFP, alpha fetoprotein; PIVKA-II, protein induced by Vitamin K absence or antagonist-II; PV, portal vein; IVC, inferior vena cava; LN, lymph node. The P values were calculated using the chi-square test or Fisher's exact test.

performed in the majority of the patients with 1–2 mm slice thickness. The gross tumor volume (GTV) was defined as PVTT or IVCTT. Delineation was performed in each phase on the 4DCT referring to the diagnostic contrast enhanced CT, magnetic resonance imaging (MRI) and angiography findings. When the primary hepatic tumor was close to the defined GTV area, it was included in the GTV if possible. The combination of multiple GTVs obtained from 4DCT was used to define the internal target volume (ITV). The planning target volume (PTV) included ITV with 2–4 mm margins considering daily set-up variations. If an OAR was very close to the target or if severe liver dysfunction existed, the PTV was usually decreased manually. Gold fiducial markers (GFM) were implanted near the target to perform tumor tracking by respiratory synchrony in all of the patients treated with CK. For TB, GFM was implanted in the majority of the patients to perform daily image-guided RT. For the remaining patients who were not implanted with GFM, iodized oil remaining after the previous TACE near the target was used as the fiducial. The gating methods were performed to account for respiratory motion.

The goal of SBRT was to deliver 45–55 Gy in 10–15 fractions. The dose that covered 95% of the PTV (PTV D95) was used as the dose prescription. Dose constraints for OAR were as follows: normal liver volume, which is defined as liver volume minus GTV, receiving a dose of more than 20 Gy (V20) must be less than 30%. The maximal dose (D_{max}) to the gastrointestinal tract was limited to 45 Gy. The maximal dose to 1 cc (D_{1cc}) was also limited to 40 Gy.

In the 3DCRT planning, patients were placed in the same position as for SBRT planning without immobilization and with free breathing. CT simulation was performed in all patients with 5 mm slice thickness without using contrast media. Definition and delineation of GTV was the same as for SBRT, also referring to the diagnostic contrast enhanced CT, MRI and angiography findings. The clinical target volume (CTV) was defined as the surrounding area of the GTV plus at most 5 mm in all directions considering the OAR, especially the duodenum. If an OAR was very close to the GTV or if severe liver dysfunction existed, the CTV was usually decreased manually, or the GTV was treated as the CTV. The PTV included the CTV plus at most a 10-mm margin in all directions considering daily set-up variations and respiratory motion of the liver.

The 3DCRT was performed with an EXL-15DP (Mitsubishi Heavy Industries, Tokyo, Japan) with free breathing. The treatment goal was 45–50 Gy in 15–25 fractions to the isocenter of the PTV. Dose constraints concerning the normal liver were the same as for

SBRT. The D_{max} for the gastrointestinal tract was limited to 40 Gy. Figure 1 shows an example of dose distribution and DVHs of CK, TB, and 3DCRT.

Evaluation

Baseline characteristics in the patients treated with CK, TB or 3DCRT were compared to identify any differences between the groups. Then, dosimetric analyses were performed and compared. As dosimetric parameters for the target, the prescribed BED₁₀, the dose that covered 98% of the PTV (PTV D98), PTV D95, the mean dose to the PTV (PTV D_{mean}), the median dose to the PTV (PTV D_{median}), the dose that covered 2% of the PTV (PTV D2), GTV size and PTV size were analyzed. As dosimetric parameters for the OAR, in addition to the normal liver V20 that was used as a dose-limited index in our institutions, the normal liver volume, the mean dose to the normal liver (Liver D_{mean}), the dose to 700 cc uninvolved normal liver, the mean dose to the right and left kidney (Right kidney D_{mean} and Left kidney D_{mean}) and intestine D_{max} were analyzed according to the recommendation in QUANTEC [19–21]. The BED₁₀ was used as the parameter instead of the total dose, because the total dose and single fraction size varied depending on the size of the tumor thrombus in order to avoid toxicity to the OAR. Dosimetric analysis in the total SBRT group was not performed, except for the prescribed BED₁₀, because the total SBRT group was composed of the CK and the TB groups, which had different dose distributions, as shown in Fig. 1. The tumor responses to RT and survival analysis were also compared between SBRT and 3DCRT, CK and 3DCRT, and TB and 3DCRT. Response was determined based on imaging performed within 6 months of the completion of RT. Post-treatment dynamic contrast enhanced CT and/or MRI were performed 3–6 weeks after the completion of RT, and every 1 to 2 months thereafter. The maximum change in the size of the tumor was used as the indicator of the response based on the World Health Organization criteria for tumor response [22].

A complete disappearance of tumor thrombi was defined as a complete response (CR), a decrease of ≥50% in thrombi size was defined as a partial response (PR), a decrease of <50% or an increase of <25% was defined as stable disease (SD) and an increase of ≥25% was defined as progressive disease (PD). Patients whose response could not be evaluated were classified as PD. Patients classified as CR and PR were defined as responders, and SD and PD were defined as non-responders. Local progression (LP) rate was defined as patients

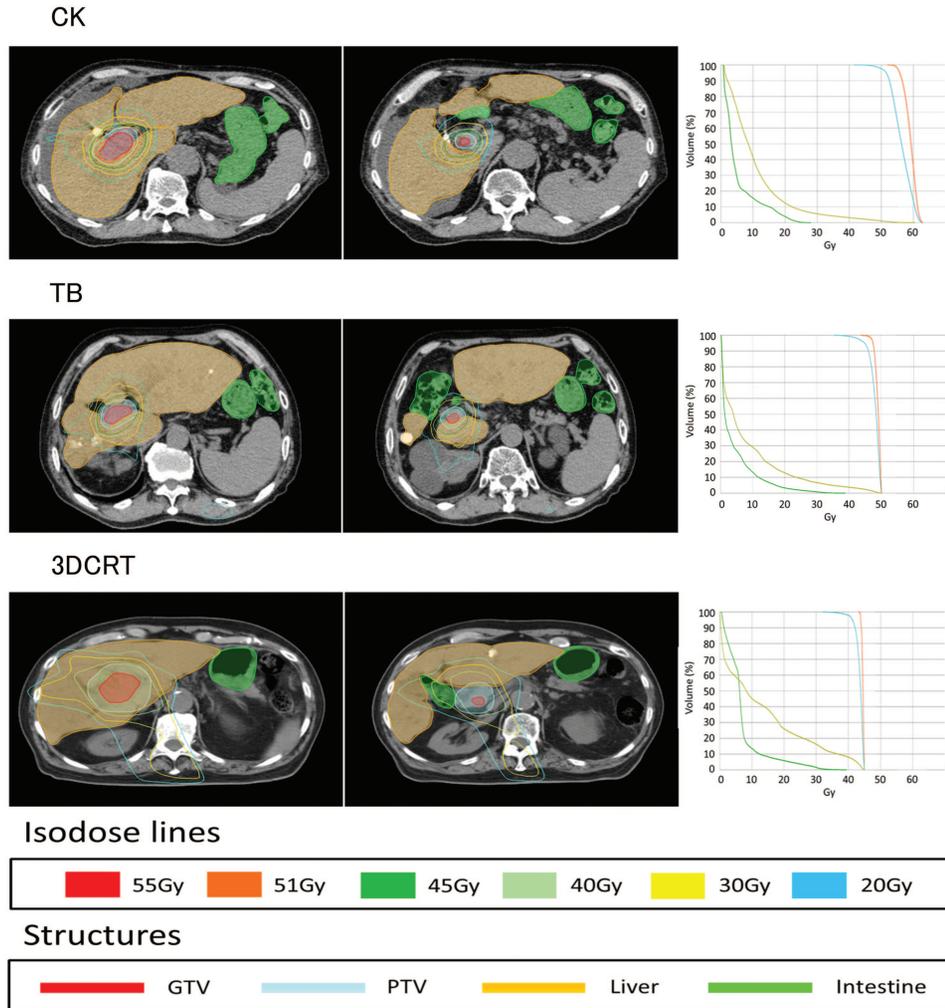


Fig. 1. An example of the dose distribution and the DVH comparing CK, TB and 3DCRT in the patients who had PVTTs invading the main trunk. A total dose of 51 Gy in 12 fractions, and of 45 Gy in 15 fractions was delivered to the PVTT using a prescription of PTV D₉₅ in the CK case and TB case, respectively. In the 3DCRT cases, 45 Gy in 15 fractions was prescribed to the isocenter of the PTV. Liver V₂₀ in CK, TB and 3DCRT was 12.5%, 13.1% and 25.9%, respectively. Normal liver D_{mean} was 11.0 Gy, 8.5 Gy and 17.3 Gy, respectively. Dose to 700 cc uninvolved liver was 9.7 Gy, 11.2 Gy, and 15.0 Gy, respectively. Intestine D_{max} was 28.0 Gy, 38.9 Gy and 39.5 Gy, respectively.

with regrowth of irradiated PVTT or IVCTT as visualized on dynamic-enhanced CT or MRI. To evaluate the effect of combined therapy, prescribed BED₁₀, treatment response and survival were evaluated and compared among those patients who received TACE, TAI and no combined therapy.

Toxicity

Toxicity induced by RT was also assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Radiation-induced liver disease (RILD) was defined as the development of nonmalignant ascites and the elevation of alkaline phosphatase levels to >2 times the pretreatment value without PD [23]. To verify late adverse effects on liver function, the deterioration in Child–Pugh score within 6 months was also evaluated in evaluable patients, defined as alive without PD or intrahepatic

recurrence, and having received no additional therapy in the 6 months after finishing RT.

Statistical analysis

All statistical analyses were performed using R (version 3.1.2, www.r-project.org) software. Categorized variables were compared using the chi-square test or Fisher's exact test, and continuous variables were compared using the Mann–Whitney *U*-test or the Kruskal–Wallis test. OS rates were calculated until the 2-year follow-up using the Kaplan–Meier method, and the differences were evaluated using the log-rank test. LP rates were also calculated until the 2-year follow-up with the cumulative incidence method, and the differences were evaluated using the Gray's test. Follow-up period was calculated from the day of RT initiation. All *P* values were two-sided, and values of less than 0.05 were considered significant.

RESULTS

Comparisons of baseline characteristics between the patients treated with CK, TB and 3DCRT

The baseline patient characteristics and comparisons between patients treated with CK, TB or 3DCRT are shown in Table 1. None of these variables was significantly different between the CK group and the 3DCRT group, or the TB group and the 3DCRT group.

Dosimetric analyses

Dosimetric analyses for CK, TB and 3DCRT were performed and were compared in Table 2. The median prescribed BED_{10} , the median total dose and the median single fraction size were 73.4 Gy₁₀, 50.4 Gy (range: 42–55 Gy) and 4.5 Gy (range: 3.0–12.5 Gy) in the total SBRT group; 75.0 Gy₁₀, 50.4 Gy (range: 42–55 Gy) and 4.5 Gy (range: 3.0–12.5 Gy) in the CK group; 60.5 Gy₁₀, 46.0 Gy (range: 36–54 Gy) and 3.2 Gy (range: 2.5–6.3 Gy) in the TB group; and 58.5 Gy₁₀, 45 Gy (range: 39–50 Gy) and 3 Gy (range: 2–3 Gy) in the 3DCRT group, respectively. Prescribed BED_{10} was significantly higher in the total SBRT group than in the 3DCRT group ($P = 0.01$), significantly higher in the CK group than in the 3DCRT group ($P < 0.001$) and significantly higher in the TB group than in the 3DCRT group ($P = 0.004$). As for the DVH parameters, each of the parameters of PTV (PTV D98, D95, D_{mean} , D_{median} and D2) were significantly higher in the CK group than in the 3DCRT group ($P < 0.001$), and also significantly higher in the TB group than in the 3DCRT group ($P < 0.001$). The size of the GTV was similar in the CK group and in the TB group compared with that in the 3DCRT groups (13.2 vs. 22.6 vs. 18.3 ml); however, the size of the PTV was smaller in the CK group than in the 3DCRT group (36.0 vs. 87.0 ml, $P < 0.001$), and also smaller in the TB group than in the 3DCRT group (51.5 vs. 87.0 ml, $P = 0.01$). Liver V20 was significantly lower in the CK group than in the 3DCRT group (12.4 vs. 25.4 Gy, $P < 0.001$). Intestine D_{max} was significantly lower in the CK group than in the 3DCRT group (25.4 vs. 36.0 Gy, $P = 0.006$). Normal liver D_{mean} , doses to 700 cc uninvolved normal liver, Right kidney D_{mean} and Left kidney D_{mean} were similar between the CK group and the 3DCRT group, and between the TB group and the 3DCRT group.

Tumor response to radiotherapy

Response to SBRT was evaluated based on the World Health Organization criteria for tumors [22] and compared with the response to 3DCRT. CR was observed in 1 (2%), PR in 28 (65%), SD in 9 (21%) and PD in 5 (12%) patients in the total SBRT group; CR in 1 (4%), PR in 18 (67%), SD in 6 (22%) and PD in 2 (7%) patients in the CK group; CR in 0 (0%), PR in 10 (62%), SD in 3 (19%) and PD in 3 (19%) patients in the TB group; and CR in 3 (6%), PR in 22 (41%), SD in 9 (21%) and PD in 5 (12%) patients in the 3DCRT group. Sixty-seven per cent (29/43 patients) in the total SBRT group, 70% (19/27 patients) in the CK group and 62% (10/16 patients) in the TB group responded (CR + PR) compared with 46% (25/54 patients) in the 3DCRT group. A significant difference was observed in the rate of response to RT between the patients treated with SBRT and 3DCRT ($P = 0.04$), and with CK and 3DCRT ($P = 0.04$).

Overall survival and local progression rate

The median follow-up period for all patients and survivors treated with SBRT was 7 months (range: 1–26 months) and 11 months

(range: 2–26 months); treated with CK was 7 months (range: 1–26 months) and 11 months (range: 2–26 months); treated with TB was 6.5 months (range: 1–26 months) and 19 months (range: 5–39 months); and treated with 3DCRT was 5.5 months (range: 0–39 months) and 7.5 months (4–39 months), respectively. Seventy-two patients had died of HCC, and 10 patients were lost to follow-up. The 1-year OS rates in the total SBRT, CK, TB and 3DCRT groups were 49.3%, 56.7%, 38.1% and 29.3%, respectively (Fig. 2a,b). The OS rate was significantly higher in the total SBRT group than in the 3DCRT group ($P = 0.02$), and also higher in the CK group than in the 3DCRT group ($P = 0.02$). The 1-year LP rates in the total SBRT, CK, TB and 3DCRT groups were 20.4%, 21.9%, 18.8% and 43.6%, respectively (Figure 2c,d). The LP rate was significantly lower in the SBRT group than the 3DCRT group ($P = 0.01$), and also lower in the CK group than in the 3DCRT group ($P = 0.04$).

Evaluation of the effects of combined therapy

Evaluation of prescribed BED_{10} , tumor response and survival with combined therapy is shown in Table 3. There was no significant difference in these factors among three groups with different combined therapies.

Toxicity

Details regarding acute adverse effects on liver function are shown in Table 4. No late gastrointestinal symptoms with severe toxicity of grade 3 or more, such as ulceration, bleeding, perforation or ileus were recorded. RILD was observed in 2 patients at 2 and 3 months after radiotherapy, and both of them were in the 3DCRT group. At 6 months after finishing RT, 12 patients were evaluable for late adverse effects on liver function. In these 12 evaluable patients, deterioration of the Child–Pugh score was observed in 1 patient treated with CK whose Child–Pugh score was 7B before RT and 8B 6 months after it.

DISCUSSION

This study aimed to clarify the efficacy of SBRT for PVTT/IVCTT from HCC compared with conventional 3DCRT. In a previous report, Lin *et al.* prospectively compared the treatment results of 3DCRT and SBRT [16]. Although 43 patients were enrolled in that study, only 14 could be evaluated because many patients in their study had a poor performance status and 29 died before the first follow-up. Therefore, the advantages of SBRT in HCC with PVTT/IVCTT could not be proven for both response and survival. No other study comparing SBRT and 3DCRT for the treatment of PVTT/IVCTT has been published to date. The current study evaluated a relatively large number of patients and included one of the largest patient cohorts ever treated with SBRT. Therefore, although this study was retrospective, it is the first and largest to compare SBRT and 3DCRT to clarify the efficacy of SBRT over 3DCRT in the treatment of PVTT/IVCTT.

Dosimetric analysis revealed that SBRT (both CK and TB) could deliver a higher BED_{10} to PVTT/IVCTT with a smaller PTV size without increasing the dose to OAR compared with 3DCRT. In this study, detailed and precise image acquisition (4DCT) and motion management (gating or fiducial tracking) were applied in SBRT. Therefore, the dosimetric advantages of SBRT should be taken into account. Previously, Underberg *et al.* demonstrated in their lung

Table 2. Comparison of dosimetric parameters between CK, TB and 3DCRT

Variables	SBRT		3DCRT (<i>n</i> = 54)	P value	
	CK (<i>n</i> = 27)	TB (<i>n</i> = 16)		CK vs. 3DCRT	TB vs. 3DCRT
Prescribed BED ₁₀ (Gy ₁₀)					
Median (range)	75.0 (58.5–112.5)	60.5 (46.8–81.25)	58.5 (46.8–60.0)	<0.001	0.004
PTV D98 (Gy)					
Median (range)	48.9 (41.4–56.8)	45.6 (35.2–53.0)	40.3 (31.8–46.6)	<0.001	<0.001
PTV D95 (Gy)					
Median (range)	50.9 (43.6–58.9)	45.9 (35.4–53.3)	41.3 (35.3–47.3)	<0.001	<0.001
PTV D _{mean} (Gy)					
Median (range)	57.6 (49.5–64.6)	48.7 (35.9–55.4)	43.6 (37.8–48.9)	<0.001	<0.001
PTV D _{median} (Gy)					
Median (range)	57.8 (50.1–65.1)	49.0 (35.9–56.1)	43.9 (38.2–49.1)	<0.001	<0.001
PTV D2 (Gy)					
Median (range)	62.1 (53.4–80.0)	50.8 (36.3–57.9)	45.0 (38.9–50.1)	<0.001	<0.001
GTV size (ml)					
Median (range)	13.2 (3.2–92.0)	22.6 (3.8–252.8)	18.3 (1.5–74.4)	0.51	0.62
PTV size (ml)					
Median (range)	36.0 (14.8–138.7)	51.5 (19.2–418.8)	87.0 (27–232.4)	<0.001	0.01
CTV/PTV margin reduced					
Yes	3 patients (11%)	4 patients (25%)	15 patients (28%)	0.09	1
No	24 patients (89%)	12 patients (75%)	39 patients (72%)		
Normal liver volume (ml)					
Median (range)	1183.3 (724.1–2179.8)	1187.2 (619.3–1512.2)	1268.4 (559.1–2301.2)	0.29	0.24
Normal liver V20 Gy (%)					
Median (range)	12.4 (3.7–33.0)	22.6 (10.6–32.0)	25.4 (8.8–40.2)	<0.001	0.09
Normal liver D _{mean} (Gy)					
Median (range)	10.7 (4.7–16.1)	11.4 (6.2–14.4)	11.8 (2.2–17.5)	0.06	0.16
Dose to 700 cc uninvolved normal liver (Gy)					
Median (range)	9.3 (0.7–49.4)	9.6 (1.1–50.7)	9.1 (0.1–41.9)	0.59	0.78
Right kidney D _{mean} (Gy)					
Median (range)	2.1 (0.0–10.6)	0.9 (0.0–6.0)	1.7 (0.0–17.9)	0.68	0.21
Left kidney D _{mean} (Gy)					
Median (range)	0.3 (0.0–2.0)	0.2 (0.0–7.5)	0.1 (0.0–5.1)	0.81	0.26
Intestine D _{max} (Gy)					
Median (range)	25.4 (6.1–43.6)	35.3 (18.9–56.8)	36.0 (2.5–49.0)	0.006	0.79

Continued

Table 2. Continued

Variables	SBRT		3DCRT (<i>n</i> = 54)	P value	
	CK (<i>n</i> = 27)	TB (<i>n</i> = 16)		CK vs. 3DCRT	TB vs. 3DCRT
Closest GI organ to the high dose area					
Stomach	5 patients	3 patients	6 patients		
Median (range) of D_{max}	17.4 (10.9–31.2)	27.2 (21.4–56.8)	33.2 (27.5–49.0)		
Duodenum	20 patients	11 patients	45 patients		
Median (range) of D_{max}	26.1 (6.1–43.6)	36.2 (18.9–47.8)	36.2 (2.5–43.2)		
Colon	2 patients	2 patients	3 patients		
Median (range) of D_{max}	26.9 (23.2–30.5)	29.9 (26.6–33.3)	31.2 (23.1–40.7)		

The *P* values were calculated using the Mann–Whitney *U*-test.

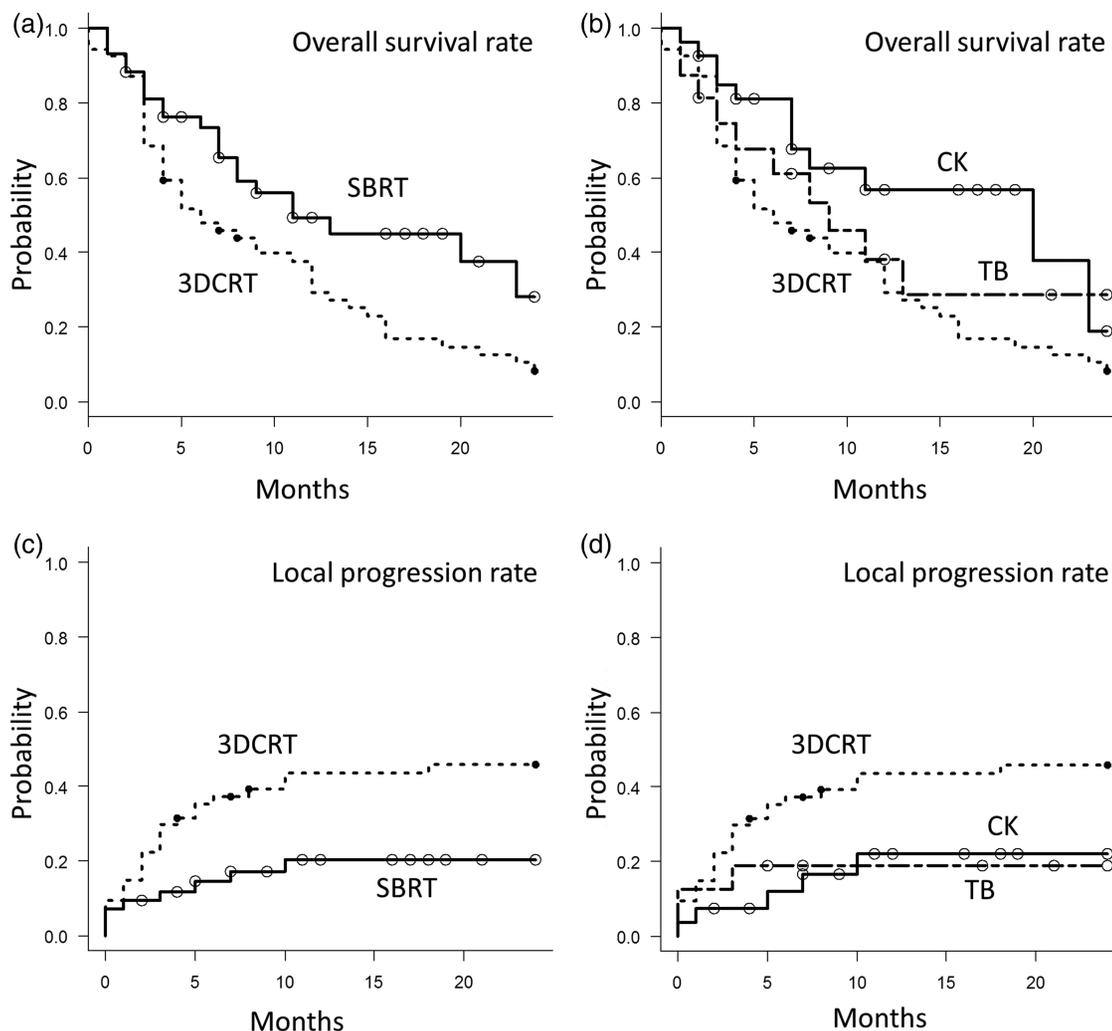


Fig. 2. OS for patients treated with SBRT and 3DCRT. (a) with CK, TB and 3DCRT. (b) LP rate of PVTT/IVCTT for patients treated with SBRT and 3DCRT. (c) With CK, TB and 3DCRT. (d) A significant difference in OS and LF rates is observed between the total SBRT group and the 3DCRT group ($P = 0.02$ and 0.01 , respectively), and between the CK group and the 3DCRT group ($P = 0.02$ and 0.04 , respectively).

Table 3. Evaluation of response and survival to combined therapy

	TACE (<i>n</i> = 30)	TAI (<i>n</i> = 32)	No. (<i>n</i> = 35)	<i>P</i> value
Prescribed BED ₁₀ (Gy ₁₀)				
Median (range)	58.5 (48.0–81.3)	58.5 (46.8–112.5)	58.5 (46.9–90.5)	0.17
Response				
Responder (CR + PR)	20 (67%)	17 (53%)	17 (49%)	0.32
Non-responders (SD + PD)	10 (33%)	15 (47%)	18 (51%)	
Survival				
MST (months)	11	5	12	0.50
1-year OS (%)	38.3	29.2	43.5	

The *P* value was calculated using the Kruskal–Wallis test in dosimetric analysis, the chi-square test in response analysis and the log-rank test in survival analysis.

Table 4. Acute adverse effects on liver function after RT

Grade	SBRT		3DCRT (<i>n</i> = 54)
	CK (<i>n</i> = 27)	TB (<i>n</i> = 16)	
Liver enzyme			
2	2 (8%)	0 (0%)	5 (9%)
3	1 (4%)	0 (0%)	1 (2%)
Bilirubin			
2	2 (8%)	0 (0%)	7 (13%)
3	0 (0%)	1 (6%)	1 (2%)
Albumin			
2	9 (33%)	5 (31%)	21 (39%)
3	0 (0%)	1 (6%)	3 (6%)
Leukocyte			
2	7 (26%)	7 (44%)	18 (33%)
3	2 (8%)	1 (6%)	5 (9%)
Platelets			
2	7 (26%)	7 (44%)	14 (26%)
3	4 (15%)	0 (0%)	3 (6%)

Toxicity was graded according to the Common Terminology Criteria for Adverse Events (version 4.0).

cancer study that planning 4DCT scans and motion management could significantly reduce PTV size and normal tissue irradiation [24]. Xi *et al.* also demonstrated in HCC cases that planning 4DCT scans could achieve a smaller PTV and lower doses to OAR and then allow dose escalation with an average increase of 7.5% compared with conventional CT scans [25]. On the basis of these studies, our dosimetric analyses were considered adequate, and we suppose that acquiring a smaller and more precise PTV compared with 3DCRT

using advanced methods such as 4DCT and motion management might contribute to the achievement of a higher BED₁₀ dose to the target and a lower dose to OAR in SBRT. Using 4DCT or breathing motion management have been used for 3DCRT for lung or liver tumors at some institutions, and using them could make it possible to prescribe a high BED₁₀ dose to the target [26, 27]. For 3DCRT for HCC with PVTT/IVCTT, to the best our knowledge there is no reported study with high BED₁₀ dosages using 4DCT or motion management even though the use of them could have the potential to improve treatment outcomes.

The benefit of prescribing a high BED₁₀ dose in improving both response and survival has been demonstrated in many previous studies [6–8, 14, 15, 28], and it also might contribute to the better tumor response, LP rate and OS in the total SBRT group and the CK group than in the 3DCRT group in this study. For 3DCRT, Kim *et al.* demonstrated that delivering a higher BED₁₀ dose resulted in a higher response rate, leading to a higher survival rate [7]. Toya *et al.* also showed that a higher response rate was observed in the higher BED₁₀ group [8]. For SBRT, Xi *et al.* reported that response and a higher dose were favorable prognostic factors [15]. In this study, SBRT delivered a significantly higher BED₁₀ (Table 2), and achieved a better response and survival rate as compared with 3DCRT (Fig. 2a–d). Although different RT techniques were compared, our results showed a similar trend to data reported in prior studies, and we can suppose that the improved efficacy in terms of SBRT response and survival rates over those of 3DCRT were correlated with the dosimetric advantages of SBRT.

The response rate, and 1-year OS rates in this study were 67% and 49.3% in the SBRT group (and 70% and 56.7% in the CK group, and 62% and 38.1% in the TB group), and 46% and 29.3% in the 3DCRT group in this study. The summary of representative previous reports is shown in Table 5. For SBRT, Xi *et al.* has also reported excellent treatment results from SBRT, with response rates and 1-year OS of 75.6% and 50.3%, respectively [15]. Although there are few published reports, response rates in studies of SBRT range from 44.4 to 75.6%, the median survival time (MST) was 8 to 13 months and the 1-year OS rate was 43.2 to 50.3%, as shown in Table 4 [14, 15]. For 3DCRT, reported response rates range from 25.2 to 45.8%, the MST was 4 to 10.6 months and the 1-year OS rates were 16.7 to 42.5% [6–8, 28].

Table 5. Published reports of clinical outcomes for PVTT/IVCTT

Author, year	Technique	No. of patients	Total dose (Gy) Median (range)	BED ₁₀ (Gy ₁₀) Median (range)	RR (%)	MST (months)	1-year OS (%)
Kim, 2005 [7]	3DCRT	59	NA (30–54)	NA (39–70.2)	46	7.8	NA
Toya, 2007 [8]	3DCRT	38	NA (17.5–50.4)	NA (23.4–59.5)	45	9.6	39.4
Huang, 2009 [6]	3DCRT	326	NA (NA–60)	NA	25	4	16.7
Yoon, 2012 [28]	3DCRT	412	NA (21–60)	51.8 (27.3–78.0)	40	10.6	42.5
Choi, 2008 [14]	SBRT	9	36 (30–36)	79.2 (60–79.2)	44	8	43.2
Xi, 2013 [15]	SBRT	41	36 (30–48)	57.6 (45–86.4)	76	13	50.3
Current study, 2015	SBRT	43	50 (36–55)	73.4 (46.8–112.5)	67	11	49.3
	3DCRT	54	45 (39–50)	58.5 (46.8–60.0)	46	6	29.3

NA, not available.

The response and survival outcomes for SBRT and 3DCRT in this study were comparable and consistent with previous reports.

Combined therapy was performed in about two-thirds of patients (TACE for 30 patients, and TAI for 32 patients) a few weeks before or after RT. In previous 3DCRT studies where TACE or TAI was performed as combination therapy, reported response rate ranged from 27.9 to 60.0% and MST was 7 to 12 months [28–30]. On the other hand, in the 3DCRT studies where RT was performed without any combined therapy, reported RR ranged from 25 to 45% and MST was 4 to 9 months [6–8]. In previous studies, although the potential of combined treatment to improve tumor control and survival was suggested, the results were based mostly on retrospective studies or a prospective study with a small number of patients, and the efficacy of this over RT alone remains unclear. In this study, to evaluate the influence of these combined therapies, prescribed BED₁₀, tumor response and survival analyses were evaluated among the three groups according to the type of combined therapy (TACE, TAI or RT alone). In the results, a significant difference in tumor response and overall survival was not recognized; nevertheless, a similar BED₁₀ was prescribed among these three groups (Table 3). Therefore, the effect of the difference of combined therapy on treatment results in this study can be considered to be negligible.

There are several possible limitations in this study. First, SBRT and 3DCRT were performed in completely different time periods. To solve this problem, a limited follow-up period was used in the survival analysis [31]. This was determined based on the prognosis of the patients with PVTT/IVCTT in previous studies. MSTs in most studies are <12 months, and the 1-year OS rate was the focus of these reports [6–8, 14, 15, 26]. Therefore, the follow-up period in the survival analysis was limited to 2 years and it was considered sufficient for this study. Second, salvage therapies such as sorafenib were not generally used for patients with PVTT/IVCTT in the early period of 3DCRT [32]. Methods for performing interventional therapy were also under development [33]. Although this study favored the survival benefit of SBRT, the development of these therapies during the period of this study might have affected its results. However, salvage or interventional therapy was not a focus of this study. Further investigation considering the effect of these therapies should be performed in the future.

Further, the total SBRT group in this study was composed of the CK group and the TB group. Therefore, each analysis was performed for the CK group and the TB group compared with 3DCRT. In addition, response rates and survival analyses were also performed in the total SBRT group compared with 3DCRT because prescribed BED₁₀ and each parameters of PTV were significantly higher both in the CK group and in the TB group when compared with 3DCRT (Table 2). As result, local control and survival in the total SBRT group were shown to be significantly superior compared with the 3DCRT group. On the other hand, when analyzing in three groups (CK vs. 3DCRT, and TB vs. 3DCRT), local control and survival in the CK group was superior to the 3DCRT group; however, none in the TB group was shown to be significantly superior compared with 3DCRT. This might be because of the dosimetric difference between the two groups, but it also may be because of the rather small number of patients in the TB group, or because of the patient's choice on treatment modality. Further experience or a prospective study is needed to clarify that issue.

In conclusion, the use of SBRT (both CK and TB) made it possible to achieve a higher BED₁₀ compared with the use of 3DCRT. Improvements in both local control and survival were also achieved in the CK group and the total SBRT group. Although further studies regarding both CK and TB evaluating a larger number of patients are needed, our results suggest that SBRT may have the potential to be the standard RT technique in the treatment of PVTT/IVCTT.

REFERENCES

1. Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. *World J Gastroenterol* 2006;47:7561–7.
2. Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999;29:62–7.
3. Georgiades CS, Hong K, D'Angelo M, et al. Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. *J Vasc Interv Radiol* 2005;16:1653–9.

4. Chern MC, Chuang VP, Liang CT, et al. Transcatheter arterial chemoembolization for advanced hepatocellular carcinoma with portal vein invasion: safety, efficacy, and prognostic factors. *J Vasc Interv Radiol* 2014;25:32–40.
5. Luo J, Guo RP, Lai EC, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. *Ann Surg Oncol* 2011;18:413–20.
6. Huang YJ, Hsu HC, Wang DY, et al. The treatment response in cases of radiation therapy to portal vein thrombosis in advanced hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2009;73:1155–63.
7. Kim DY, Park W, Lim DH, et al. Three-dimensional conformal radiotherapy for portal vein thrombosis of hepatocellular carcinoma. *Cancer* 2005;103:2419–26.
8. Toya R, Murakami R, Baba Y, et al. Conformal radiation therapy for portal vein tumor thrombosis of hepatocellular carcinoma. *Radiother Oncol* 2007;84:266–71.
9. Zeng ZC, Fan J, Tang ZY, et al. A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus. *Int J Radiat Oncol Biol Phys* 2005;61:432–43.
10. Katamura Y, Aikata H, Takaki S, et al. Intra-arterial 5-fluorouracil/interferon combination therapy for advanced hepatocellular carcinoma with or without three-dimensional conformal radiotherapy for portal vein tumor thrombosis. *J Gastroenterol* 2009;44:492–502.
11. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2011;81:e447–53.
12. Sanuki N, Takeda A, Oku Y, et al. Stereotactic body radiotherapy for small hepatocellular carcinoma: a retrospective outcome analysis in 185 patients. *Acta Oncol* 2014;53:399–404.
13. Huertas A, Baumann AS, Saunier-Kubs F, et al. Stereotactic body radiation therapy as an ablative treatment for inoperable hepatocellular carcinoma. *Radiother Oncol* 2015;115:211–16.
14. Choi BO, Choi IB, Jang HS, et al. Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: preliminary analysis. *BMC Cancer* 2008;8:351.
15. Xi M, Zhang L, Zhao L, et al. Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. *PLoS One* 2013;8:e63864.
16. Lin CS, Jen YM, Chiu SY, et al. Treatment of portal vein tumor thrombosis of hepatoma patients with either stereotactic radiotherapy or three-dimensional conformal radiotherapy. *Jpn J Clin Oncol* 2006;36:212–17.
17. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208–36.
18. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–55.
19. Pan CC, Kavanagh BD, Dawson LA, et al. Radiation-associated liver injury. *Int J Radiat Oncol Biol Phys* 2010;76:S94–100.
20. Dawson LA, Kavanagh BD, Paulino AC, et al. Radiation-associated kidney injury. *Int J Radiat Oncol Biol Phys* 2010;76:S108–15.
21. Kavanagh BD, Pan CC, Dawson LA, et al. Radiation dose-volume effects in the stomach and small bowel. *Int J Radiat Oncol Biol Phys* 2010;76:S101–7.
22. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. *Cancer* 1981;47:207–14.
23. Lawrence TS, Dworzanin LM, Walker-Andrews SC, et al. Treatment of cancers involving the liver and porta hepatis with external beam irradiation and intraarterial hepatic fluorodeoxyuridine. *Int J Radiat Oncol Biol Phys* 1991;20:555–61.
24. Underberg RW, Lagerwaard FJ, Slotman BJ, et al. Benefit of respiration-gated stereotactic radiotherapy for stage I lung cancer: an analysis of 4DCT datasets. *Int J Radiat Oncol Biol Phys* 2005;62:554–60.
25. Xi M, Liu MZ, Deng XW, et al. Defining internal target volume (ITV) for hepatocellular carcinoma using four-dimensional CT. *Radiother Oncol* 2007;84:272–8.
26. Rosenzweig KE, Fox JL, Yorke E, et al. Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable nonsmall cell lung carcinoma. *Cancer* 2005;103:2118–27.
27. Huang BS, Tsang NM, Lin SM, et al. High-dose hypofractionated X-ray radiotherapy for hepatocellular carcinoma: Tumor responses and toxicities. *Oncol Lett* 2013;6:1514–20.
28. Yoon SM, Lim YS, Won HJ, et al. Radiotherapy plus transarterial chemoembolization for hepatocellular carcinoma invading the portal vein: long-term patient outcomes. *Int J Radiat Oncol Biol Phys* 2012;82:2004–11.
29. Chuma M, Taguchi H, Yamamoto Y, et al. Efficacy of therapy for advanced hepatocellular carcinoma: intra-arterial 5-fluorouracil and subcutaneous interferon with image-guided radiation. *J Gastroenterol Hepatol* 2011;26:1123–32.
30. Yamada K, Izaki K, Sugimoto K, et al. Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2003;57:113–19.
31. Jeppesen SS, Schytte T, Jensen HR, et al. Stereotactic body radiation therapy versus conventional radiation therapy in patients with early stage non-small cell lung cancer: an updated retrospective study on local failure and survival rates. *Acta Oncol* 2013;52:1552–8.
32. Nagai H, Mukozu T, Ogino YU, et al. Sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombus. *Anticancer Res* 2015;35:2269–77.
33. Zhou X, Tang Z, Wang J, et al. Doxorubicin-eluting beads versus conventional transarterial chemoembolization for the treatment of hepatocellular carcinoma: a meta-analysis. *Int J Clin Exp Med* 2014;7:3892–903.