

The Safety Indicator of Radiotherapy for Advanced Hepatoma with Liver Cirrhosis

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Received: May 8, 2013

Revised: June 11, 2013

Accepted: June 12, 2013

Published online: August 21, 2013

ABSTRACT

AIM: To identify the dose-volumetric parameters (DVPs) associated with the risk of radiation-induced liver disease (RILD) or Child-Pugh score deterioration (CPSD) in hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (PVTT) treated with single photon emission computed tomography-based three-dimensional conformal radiotherapy (SPECT-B 3DCRT).

METHODS: A total of 64 HCC patients with PVTT underwent SPECT-B3DCRT (total dose of 45 Gy/18 fractions). SPECT using Tc-99m-galactosyl human serum albumin enabled the minimum possible irradiation of functional liver (FL). RILD or CPSD was scored within 4 months of completing SPECT-B3DCRT. The following DVPs were analyzed: mean dose to FL; mean dose to normal liver (NL); percentage of FL volume receiving ≥ 20 , ≥ 25 , and ≥ 30 Gy; percentage of NL volume receiving ≥ 20 , ≥ 25 , and ≥ 30 Gy; and percentage of total liver volume receiving ≥ 20 , ≥ 25 , and ≥ 30 Gy.

RESULTS: Of the 64 patients, RILD or CPSD by 1 was observed in 3 (4.7%) or 12 (18.8%) patients, respectively. Multivariate analysis for predicting RILD or CPSD revealed FL volume receiving ≥ 20 Gy (FLV_{20Gy}) as the only significant parameter ($p < 0.001$). The observed rates of $FLV_{20Gy} \leq 20\%$ and $FLV_{20Gy} > 20\%$ for RILD or CPSD by 1 were 4.5% (2/44) and 65% (13/20), respectively ($p < 0.001$).

CONCLUSION: $FLV_{20Gy} \leq 20\%$ appears to be a predictive indicator for avoiding the risk of RILD or CPSD by 1.

Key words: Functional image-guided radiotherapy; Three-dimensional conformal radiotherapy; Hepatocellular carcinoma; Portal vein tumor thrombus; Dose-volumetric parameters

Shirai S, Sato M, Noda Y, Kumayama Y, Sonomura T, Kawai N, Minamiguchi H, Nakai M, Sanda H, Tanaka F. The Safety Indicator of Radiotherapy for Advanced Hepatoma with Liver Cirrhosis. *Journal of Gastroenterology and Hepatology Research* 2013; 2(8): 730-736 Available from: URL: <http://www.ghmet.org/index.php/joghr/article/view/454>

INTRODUCTION

The occurrence of radiation induced liver disease (RILD) after radiation therapy (RT) for hepatocellular carcinoma (HCC) remains a serious problem^[1,2]. Associated Child-Pugh class B (Child B) liver cirrhosis and hepatitis B virus infection are reported as negative causative factors for RILD^[1,2]. Clues towards overcoming RILD are previously documented as cut-off values for dose volumetric parameters based on total liver (TL) volume^[3,4]. In short, Yamada *et al*^[3] described total liver volume receiving ≥ 30 Gy of less than 40% ($TLV_{30Gy} < 40\%$) as a safety indicator for avoiding RILD, while Kim *et al*^[4] described $TLV_{30Gy} < 60\%$ as that for avoiding radiation-induced hepatic toxicity. RT is still required to treat gigantic HCC^[5]. However, when tumor size increases to more than 40% or 60% of total liver volume, the safety of RT cannot be assured using dose volumetric parameters based on total liver volume. For these reasons, we attempted to construct a safety indicator that uses normal liver (NL) instead of total liver.

The purpose of this study is to create a safety indicator for RT for HCC, using functional NL data.

MATERIALS AND METHODS

This clinical investigation was approved by the Ethics Committee of our institute, and informed consent was obtained from all patients. The study procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2000. The eligibility criteria comprised the following: (1) unresectable HCC with portal vein tumor thrombus (PVTT) in the 1st branch and/or the main trunk; (2) no limit to HCC size; (3) the absence of extrahepatic metastasis; (4) no ascites or under medical control of ascites; (5) 5-9 points on Child-Pugh class A or B (Child A or B); and (6) performance status

of between 0 and 2 on the Eastern Cooperative Oncology Group scale. HCC with PVTT was diagnosed based on the guidelines of the Liver Cancer Study Group of Japan^[6]. Prior to RT, transcatheter arterial chemoembolization (TACE) using 3-10 mL lipiodol with or without gelatin sponge particles was performed in each case. As anticancer drugs, 40-60 mg of epirubicin hydrochloride and 10 mg mitomycin C were mixed with lipiodol. TACE using lipiodol (TACE-Lp) was attempted for the whole tumor and TACE using lipiodol and gelatin sponge particles (TACE-Lp and GSP) was performed super-selectively for tumor outside the main tumor and PVTT. In brief, main tumor and PVTT were treated by TACE-Lp, and intrahepatic metastases were treated by TACE-Lp and GSP. TACE-Lp was expected to control minute HCC surrounding the main tumor and PVTT^[7].

SPECT Analysis

Tc-99m-galactosyl human serum albumin (GSA) SPECT^[8] was performed using a double-headed camera (INFINIA: GE Medical System, USA). Tc-99m-GSA (185 MBq) was injected as an intravenous bolus via a cubital vein. SPECT data (90 steps, 360 degree) were obtained for 20 minutes with image matrix 128×128 and zoom 1.28. Image reconstruction was conducted using ordered subset expectation maximization (OSEM) method and Chang's attenuation correction^[9].

Identification of Functional Liver Volume

Functional liver volume (FLV) was distinguished from normal liver volume (NLV) prior to radiation planning. For accuracy, Tc-99m-GSA SPECT^[8], dynamic contrast-enhanced CT, and simulation CT were performed within no longer than 2 weeks before three-dimensional conformal RT (3DCRT). To enable accurate fusion of the images, all images of the whole liver in each modality were obtained with 5-mm thickness under breath holding at end-expiration. We contoured the whole liver, main tumor, PVTT, and other hepatic tumors (intrahepatic metastases) on the dynamic CT images of each patient. We defined NLV as the area remaining after subtracting the main tumor plus PVTT plus other hepatic tumors from the whole liver. Within NLV, areas that had the same radioisotope (RI) filling defects as that of HCC were defined as dysfunctional liver volume (dys-FLV); areas of hyper-accumulation relative to HCC were defined as FLV^[8]. The corresponding areas on SPECT images were then outlined on the dynamic CT images, and these transferred areas were fused with the corresponding simulator CT images and outlined.

Radiation planning and radiation therapy

Our 3DCRT method is summarized as follows. All patients underwent 3DCRT in the supine position with both arms raised above the head. We used no special apparatus for respiratory immobilization. To minimize the effects of respiration, the subjects practiced breath holding for 10-15 s at the time of end-expiration until the position could be maintained within 5 mm under X-ray fluoroscopic monitoring. RT using a 10 MV linear accelerator was repeatedly delivered during breath holding at end-expiration for 10-15 s at a time.

Simulation CT data were transferred to a three-dimensional radiation treatment planning system (Pinnacle, ADAC Laboratories, Milpitas, CA); subsequent CT treatment planning is shown in figure 1. Gross tumor volume (GTV) was defined as main tumor plus PVTT. Because tumor outside GTV was expected to be controlled by TACE, clinical target volume (CTV) was regarded the same as GTV. Planning target volume (PTV) included CTV with a 10-mm margin:

5 mm to allow for respiratory-induced motion and 5 mm to allow for penumbra covering and variations in daily setup.

The optimal 3DCRT beam directions (optimal angles of the gantry) were explored using the SPECT images for guidance as proposed by Shirai *et al.*^[10,11]. The directions of the two high-dose beams were designed to cover primarily the main tumor and PVTT, and to irradiate FLV as little as possible^[10,11]. As shown in figure 1, doses of the high-dose beams were limited to 38.25 Gy/18 fractions/4 weeks to prevent adverse effects to the duodenum, spinal cord, and kidneys^[12,13]. Three additional low-dose beams of 6.75 Gy/18 fractions/4 weeks were required to elevate the dose to the CTV, resulting in a total dose of 45 Gy to the isocenter^[14]. These low-dose beams were designed to avoid irradiating risk organs such as the stomach, duodenum, and spinal cord. Doses of 2.25 Gy for each additional beam did not cause liver damage even if the beams irradiated FLV^[10,11]. In terms of the kidney, the volume irradiated at 20 Gy or more was planned to not exceed 30% of the total volume. Finally, the couch angle was adjusted to the maximum limit of 90.

Follow-up evaluation

All patients underwent follow-up CT at 1 month after RT. Follow-up SPECT using Tc-99m-GSA was performed 2 months after completion of SPECT-B3DCRT. Laboratory tests for blood and liver function were conducted weekly during SPECT-B3DCRT and monthly for 4 months after the completion of SPECT-B3DCRT, according to the definition of the radiation induced liver disease created by Pan *et al.*^[15]. If changes in transaminase or other factors levels were detected, the tests were rechecked after an interval of 1-2 weeks. Follow-up SPECT was feasible to determine radiation-induced dysfunctional liver volume (radiation-induced dys-FLV) (Figure 1-F)^[11]. Because previous studies by Shirai *et al.*^[10,11] showed that the border between radiation-induced dys-FLV and remaining FLV was situated between the 20- and 30-Gy iso-dose curves, we focused on the 20, 25, and 30 Gy areas of the iso-dose curve for analysis of dose-volumetric parameters.

Radiation-induced liver disease (RILD) and Child-Pugh score (CPS) deterioration

Classic and non-classic RILD were assessed according to the endpoints of RILD described by Pan *et al.*^[15]. Classic RILD involves anicteric hepatomegaly and ascites, as well as elevated alkaline phosphatase (more than twice the upper limit of the normal or baseline value). Non-classic RILD involves elevated liver transaminase (more than five times the upper limit of normal, or 20 times the upper limit of normal in patients with baseline transaminase values more than five times the upper limit of the normal range) or a decline in liver function (defined as a worsening of CPS by 2 or more), within 4 months after completion of RT.

Because mild RILD but no cases of severe RILD were observed after SPECT-B3DCRT^[10,11], in the present study we added CPS deterioration by 1 to the RILD definition to investigate hepatic toxicity after SPECT-B3DCRT. Namely, all patients were evaluated for evidence of RILD or CPS deterioration by 1 within 4 months after completion of RT. This process excluded from the study all patients who had progressive disease (PD) within 4 months after 3DCRT.

Risk factors related to RILD and CPS deterioration

Clinical parameters and dose volumetric parameters were investigated as risk factors. The 14 clinical parameters were as follows: gender, age, performance status (PS), PVTT, hepatitis virus type, alpha-fetoprotein (AFP), Child-Pugh class, the Cancer of the Liver Italian

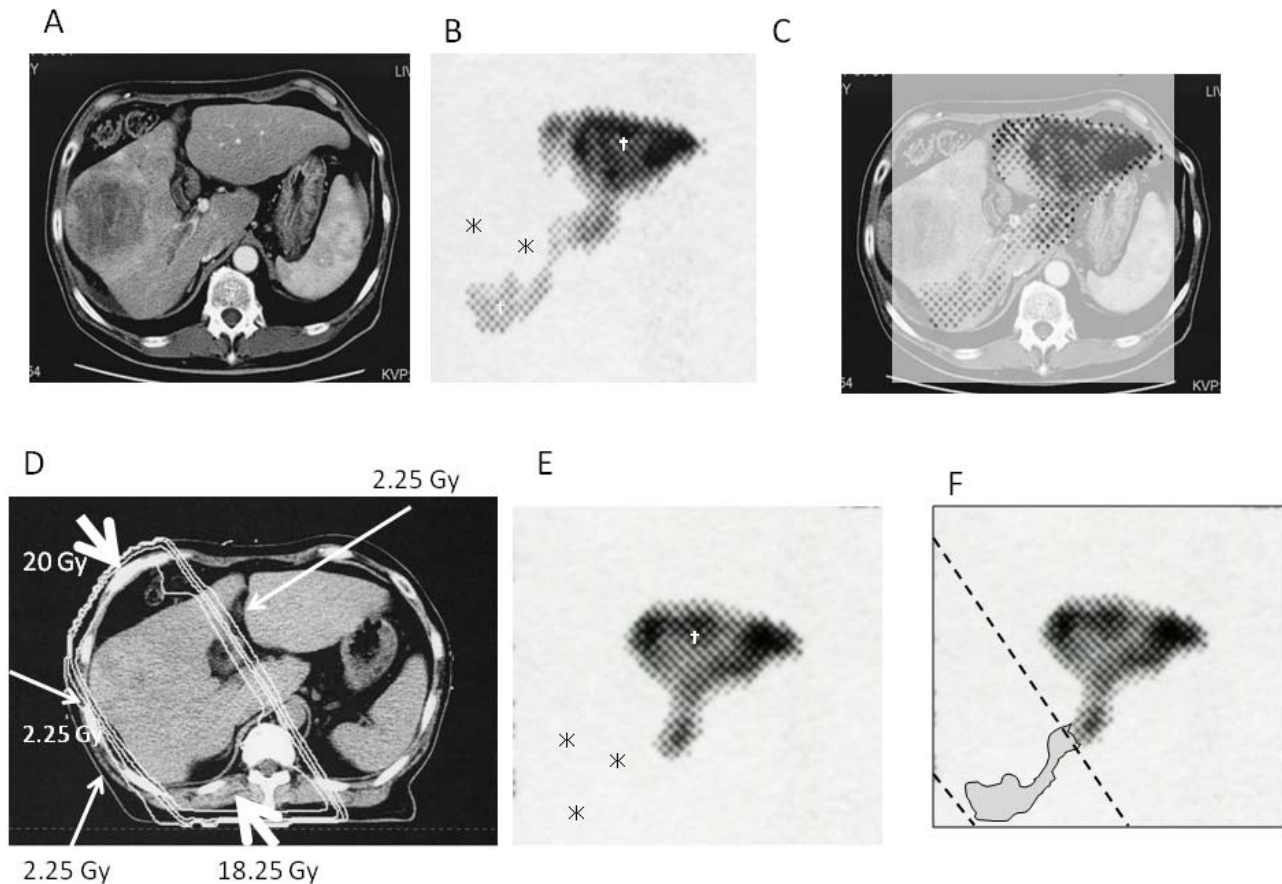


Figure 1 Images of a 62-year-old man with hepatocellular carcinoma. Contrast-enhanced computed tomography (CT) (A), single photon emission computed tomography (SPECT) using Tc-99m-galactosyl human serum albumin before radiotherapy (RT) (B), fusion image of A and B (C), dose distribution on simulation CT (D), and SPECT after RT (E, F). In (B), regions of non-accumulation (*) correspond to the main tumor and portal vein tumor thrombus (PVTT); regions of high accumulation (†) correspond to functional liver (FL). These regions were identified by the fusion image (C). SPECT obtained 2 months after completion of RT delineates regions of non-accumulation (*) along the two high-dose beams, with preservation of FL (†) (E). Comparing (B) with (E), radiation-induced dysfunctional liver is shown as the gray area outlined in black (F).

Program (CLIP) scoring system^[16], previous treatment, GTV, FLV, NLV, TLV, and GTV/TLV. The 12 dose volumetric parameters were as follows: mean dose to functional liver (mean dose to FL), mean dose to normal liver (mean dose to NL); the percentage of functional liver volume receiving ≥ 20 Gy (FLV_{20Gy}), ≥ 25 Gy (FLV_{25Gy}), and ≥ 30 Gy (FLV_{30Gy}); the percentage of normal liver volume receiving ≥ 20 Gy (NLV_{20Gy}), ≥ 25 Gy (NLV_{25Gy}), and ≥ 30 Gy (NLV_{30Gy}); the percentage of total liver volume receiving ≥ 20 Gy (TLV_{20Gy}), ≥ 25 Gy (TLV_{25Gy}), and ≥ 30 Gy (TLV_{30Gy}); and normal tissue complication probability (NTCP) estimates. NTCP estimates were derived from the Lyman model using the effective volume method^[17]. In the Lyman model, the tolerance dose for 50% complications for uniform whole organ irradiation (TD50), m (the steepness of the dose-response at TD50), and n (the volume effect parameter) were 40 Gy, 0.15, and 0.32, respectively^[17,18].

Statistical analysis

Gender (male vs. female), age (≤ 60 vs. >60 years), PS (0-1 vs. 2), PVTT (major branch vs. trunk), hepatitis B virus (no vs. yes), serum level of AFP (<400 vs. ≥ 400 IU/mL), Child-Pugh class (A vs. B), CLIP score (<3 vs. ≥ 3), previous treatment (TACE-Lp vs. TACE-Lp and GSP), and RILD or CPS deterioration by 1 (no vs. yes) were considered binary variables. GTV, FLV, NLV, TLV, GTV/TLV, and dose-volumetric parameters (mean dose to FL, mean dose to NL, FLV_{20Gy} , FLV_{25Gy} , FLV_{30Gy} , NLV_{20Gy} , NLV_{25Gy} , NLV_{30Gy} , TLV_{20Gy} , TLV_{25Gy} , TLV_{30Gy} , and NTCP) were analyzed as continuous variables. Patients were classified according to RILD or CPS deterioration

by 1 (no vs. yes). Univariate logistic regression analysis was used to compare the patients with RILD or CPS deterioration by one to those without in terms of clinical parameters and dose-volumetric parameters. Spearman's rank and Pearson's correlation coefficient tests were used to assess correlations between clinical parameters and dose-volumetric parameters. Multivariate analysis in a stepwise procedure was used to evaluate any associations between RILD or CPS deterioration by 1 and the clinical parameters or dose-volumetric parameters; a logistic regression model was used, containing all significant variables according to the univariate logistic regression analysis. Estimated probability values, receiver-operating characteristic (ROC) curve, and Fisher's exact test were used to predict the cut-off point for RILD or CPS deterioration by 1. Statistical tests were two-sided and were performed using SPSS version 11.0 (SPSS Inc., Chicago, IL). A *p* value of <0.05 was considered to indicate significant difference.

RESULTS

Seventy-seven patients underwent TACE plus SPECT-B3DCRT for HCC with PVTT of the 1st branch and/or main portal trunk between May 2008 and April 2011. The data were analyzed in September 2011. Of the 77 cases, 3 cases with total dose of less than 45 Gy and 10 cases with PD within 4 months after 3DCRT were withdrawn from the study. The remaining 64 cases were enrolled in the study. In all cases, RT was completed and adequate SPECT images were acquired before and 2 months after RT for quantitative analysis. A

borderline (dashed lines in figure 1-F) was clearly seen between radiation-induced dys-FL and the remaining FL after 3DCRT; on every SPECT slice, this borderline was observed between the 20 and 30 Gy iso-dose curves. The median follow-up period was 9.4 months (range, 4.1-40.3 months).

Patient backgrounds and tumor characteristics are listed in table 1. Regarding the other clinical parameters, mean GTV, FLV, NLV, TLV, and GTV/TLV were 415±554.1 cm³ (range, 20-2279), 931.2±265.5 cm³ (range, 223-1779), 1076.2±275.5 cm³ (range, 516-1976), 1599.9±680.0 cm³ (range, 615-4002), and 20.4%±18.7% (range, 1.7-63.7), respectively.

Table 1 Patient characteristics.

Characteristic	Value
Gender	
Male	54 (84.4)
Female	10 (15.6)
Age (years)	
Median	69.5
Range	42-87
≤60	19 (29.7)
>60	45 (70.3)
Performance status	
0	20 (31.3)
1	31 (48.4)
2	13 (20.3)
PVTT	
Major branch	36 (56.3)
Truncus	28 (43.7)
Hepatitis virus type	
HBV	17 (26.5)
HCV	34 (53.1)
Both	4 (6.3)
Unknown	9 (14.1)
AFP (IU/mL)	
<400	36 (56.3)
≥400	28 (43.7)
Child-Pugh class	
A	34 (53.1)
B	30 (46.9)
CLIP score	
1	14 (21.9)
2	17 (26.5)
3	18 (28.1)
4	12 (18.8)
5	3 (4.7)
Previous treatment	
TACE-Lp	21 (32.8)
TACE-Lp and GSP	43 (67.2)

PVTT: portal vein tumor thrombus; HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: α -fetoprotein; CLIP: Cancer of the Liver Italian Program; TACE-Lp: transcatheter arterial chemoembolization with lipiodol; TACE-Lp and GSP: transcatheter arterial chemo-embolization with lipiodol plus gelatin sponge particles. Data are presented as number of patients, with percentages in parentheses.

Of the 64 patients, CPS deterioration by 1 occurred in 12 patients and CPS deterioration by 2 occurred in 3 patients, corresponding to RILD. No patient experienced RILD by other criteria or CPS deterioration by 3 or greater. No fatal RILD developed. The interval from RT completion to the occurrence of CPS deterioration ranged from 1 to 8 weeks (median, 4 weeks). All patients recovered from CPS deterioration, and the duration time of CPS deterioration was 1-16 weeks (median, 8 weeks).

The results of univariate analysis of the association between the clinical and dose-volumetric parameters and RILD or CPS deterioration by 1 are summarized in tables 2 and 3, respectively. None of the 14 clinical parameters was associated with a risk of RILD or CPS deterioration by 1. All 12 dose-volumetric parameters were associated with a risk of RILD or CPS deterioration by 1. The dose-volumetric parameters all correlated closely with each other (mean dose to

Table 2 Univariate analysis of clinical parameters associated with risk of radiation induced liver disease (RILD) or Child-Pugh score deterioration (CPSD).

Characteristic	RILD or CPSD		p ¹
	No (n=49)	Yes (n=15)	
Gender (n)			
Male	42	12	0.596
Female	7	3	
Age (years)			
≤60	15	4	0.770
>60	34	11	
Performance status			
0-1	41	10	0.160
2	8	5	
PVTT			
Major branch	26	10	0.356
Truncus	23	5	
HBV			
No	34	9	0.500
Yes	15	6	
AFP (IU/mL)			
<400	29	7	0.395
≥400	20	8	
Child-Pugh class			
A	29	5	0.086
B	20	10	
CLIP score			
<3	27	4	0.062
≥3	22	11	
Previous treatment			
TACE-Lp	15	6	0.500
TACE-Lp & GSP	34	9	
GTV (cm ³)	367.1±545.3	572.6±572.2	
Functional liver volume (cm ³)	925.2±276.9	950.7±232.1	0.744
Normal liver volume (cm ³)	1088.7±291.6	1035.3±218.4	0.510
Total liver volume (cm ³)	1564.5±690.8	1715.3±652.5	0.453
GTV/Total liver volume (%)	18.0±18.3	28.2±18.7	0.069

RILD: radiation-induced liver disease; CPSD: Child-Pugh score deterioration; GTV: gross tumor volume; other abbreviations as in table 1. Data are presented as number of patients or mean±standard deviation. ¹ Univariate logistic regression analysis.

Table 3 Univariate analysis of dose-volumetric parameters associated with risk of radiation induced liver disease (RILD) or Child-Pugh score deterioration (CPSD).

Characteristic	RILD or CPSD		p ¹
	No (n=49)	Yes (n=15)	
MDTFL (Gy)	9.9±2.4	13.4±2.6	<0.001
MDTNL (Gy)	11.4±2.3	14.0±3.1	0.004
FLV _{20Gy} (%)	14.7±4.2	24.3±5.1	<0.001
FLV _{25Gy} (%)	13.0±4.3	21.3±4.8	<0.001
FLV _{30Gy} (%)	11.0±3.6	18.6±4.3	<0.001
NLV _{20Gy} (%)	18.8±5.8	27.2±7.3	0.001
NLV _{25Gy} (%)	17.1±4.6	23.9±6.7	0.001
NLV _{30Gy} (%)	14.4±4.2	20.8±6.0	0.001
TLV _{20Gy} (%)	35.8±17.9	49.2±18.8	0.021
TLV _{25Gy} (%)	33.7±18.1	46.9±19.0	0.023
TLV _{30Gy} (%)	31.8±18.1	44.8±19.0	0.025
NTCP (%)	0.24±0.52	0.93±1.10	0.009

RILD: radiation-induced liver disease; CPSD: Child-Pugh score deterioration; MDTFL: mean dose to functional liver; MDTNL: mean dose to normal liver; FLV_{20Gy}, FLV_{25Gy}, and FLV_{30Gy}: percentage of functional liver volume receiving ≥20, ≥25, and ≥30 Gy, respectively; NLV_{20Gy}, NLV_{25Gy}, and NLV_{30Gy}: percentage of normal liver volume receiving ≥20, ≥25, and ≥30 Gy, respectively; TLV_{20Gy}, TLV_{25Gy}, and TLV_{30Gy}: percentage of total liver volume receiving ≥20, ≥25, and ≥30 Gy, respectively; NTCP=normal tissue complication probability. Data are presented as mean±standard deviation. ¹ Univariate logistic regression analysis.

NL vs. mean dose to FL, $r = 0.882$, $p < 0.001$; mean dose to NL vs. FLV_{20Gy}, $r = 0.689$, $p < 0.001$; mean dose to NL vs. FLV_{25Gy}, $r = 0.748$, $p < 0.001$; mean dose to NL vs. FLV_{30Gy}, $r = 0.721$, $p < 0.001$; mean dose to NL vs. NLV_{20Gy}, $r = 0.851$, $p < 0.001$; mean dose to NL vs. NLV_{25Gy}, $r = 0.899$, $p < 0.001$; mean dose to NL vs. NLV_{30Gy}, $r = 0.842$, $p < 0.001$; mean dose to NL vs. TLV_{20Gy}, $r = 0.766$, $p < 0.001$; mean dose to NL

vs. TLV_{25Gy} , $r=0.757$, $p<0.001$; mean dose to NL vs. TLV_{30Gy} , $r=0.748$, $p<0.001$; and mean dose to NL vs. NTCP, $r=0.720$, $p<0.001$).

Multivariate analysis revealed FLV_{20Gy} as the only parameter significantly associated with a risk of RILD or CPS deterioration by 1 ($p<0.001$).

Figure 2 shows the estimated probability values for CPS deterioration by 1 or 2 according to FLV_{20Gy} . When FLV_{20Gy} was 20%, the probability of RILD or CPS deterioration by 1 increased steeply. As shown in figure 3, the area under the receiver-operating characteristic curve was 0.923 ($p<0.001$), and it would be appropriate to consider FLV_{20Gy} of 20% as a cutoff point for predicting RILD or CPS deterioration by 1. With FLV_{20Gy} of 20%, the accuracy for predicting RILD or CPS deterioration by 1 was 0.859 (55 of 64), with sensitivity of 0.867 and specificity of 0.857. The observed rates of $FLV_{20Gy} \leq 20\%$ and $FLV_{20Gy} > 20\%$ for RILD or CPS deterioration by 1 were 4.5% (2/44) and 65% (13/20), respectively ($p<0.001$). The observed rates of $TLV_{30Gy} \leq 40\%$

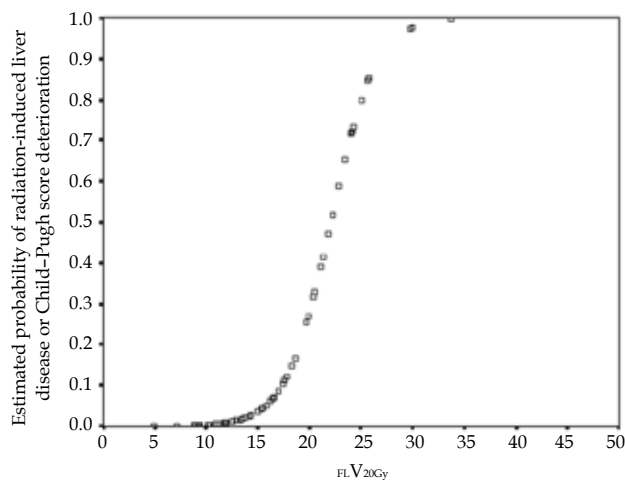


Figure 2 Estimated probability values of radiation-induced liver disease (RILD) or Child-Pugh score (CPS) deterioration by 1 according to percentage of functional liver volume receiving ≥ 20 Gy (FLV_{20Gy}). Probability values were estimated based on logistic regression analysis.

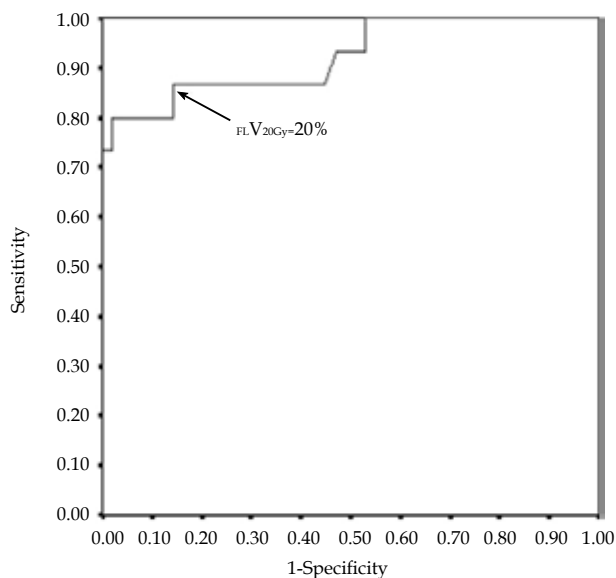


Figure 3 Receiver-operating characteristic (ROC) curve generated by percentage of functional liver volume receiving ≥ 20 Gy (FLV_{20Gy}). The tolerance cutoff point of FLV_{20Gy} was 20%. At FLV_{20Gy} of 20%, sensitivity and specificity were 0.867 and 0.857, respectively, for prediction of radiation induced liver disease (RILD) or Child-Pugh score (CPS) deterioration by 1. Area under the receiver-operating characteristic curve was 0.923 ($p<0.001$).

and $TLV_{30Gy} > 40\%$ for RILD or CPS deterioration by 1 were 17.1% (7/41) and 34.8% (8/23), respectively ($p=0.132$). Furthermore, those of $TLV_{30Gy} \leq 60\%$ and $TLV_{30Gy} > 60\%$ for RILD or CPS deterioration by 1 were 20.4% (11/54) and 40% (4/10), respectively ($p=0.226$).

Adverse effects on skin, upper gastrointestinal tract and whole blood were analyzed based on Common Terminology Criteria for Adverse events v3.0. Grade 1 for skin in 10 cases (10/64, 15.6%) and Grade 1 for gastrointestinal tract in 8 cases (8/64, 12.5%) were obtained. As for the whole blood, Grade 1, 2, and 3 for white blood cells were obtained in 8 cases (8/64, 12.5%), 13 cases (13/64, 20.3%), and 4 cases (4/64, 6.3%), respectively and Grade 1, 2, and 3 for platelets, in 12 cases (12/64, 18.8%), 6 cases (6/64, 9.4%), and 5 cases (5/64, 7.8%), respectively. All cases with Grade 3 worsened from Grade 2 before RT.

All these adverse events were transient and reversible.

DISCUSSION

Prior to SPECTB-3DCRT, TACE using lipiodol was the primary method for controlling microscopic tumor invasion around the main tumor and PVTT^[7]. For this reason, in the present study we defined CTV for radiation planning as the same area as GTV. Analysis of SPECT following RT with reference to the dose distribution on simulation CT clarified that the borderline detected between radiation-induced dys-FL and FL was equivalent to the interval between the 20 Gy and 30 Gy iso-dose curves in each patient. This finding implies that irradiation under breath-holding at end-expiration was performed correctly. We consider that radiation planning with a 10-mm margin surrounding the GTV was valid, although a margin of more than 10 mm is documented in previous 3DCRT studies^[1-4].

This set-up using a narrow margin led to decreased dose volumetric parameters values and average NTCP^[17,18], with the endpoint at liver failure of less than 1% (Table 3). The observed rate of $FLV_{20Gy} \leq 20\%$ (4.5%) for RILD or CPS deterioration by 1 was significantly less than that of $FLV_{20Gy} > 20\%$ (65%) ($p<0.001$). $FLV_{20Gy} = 20\%$ was determined as the cutoff point by multivariate analysis, estimated probability values, and ROC curve. This cutoff point should be viewed as the point at which RT adverse effects to the liver may occur to the degree of CPS deterioration by 1, rather than the point at which severe RILD would occur. SPECTB-3DCRT was conducted with the aim of covering the main tumor plus PVTT, and also irradiating FL as little as possible. The cutoff points of $TLV_{30Gy} = 40\%$ ^[3] and $TLV_{30Gy} = 60\%$ ^[4] proposed by Yamada *et al* and Kim *et al*, respectively, did not show statistical significance in the present study ($p=0.132$ and $p=0.226$, respectively). This difference may be dependent on the patient backgrounds, selection of the main beam, and liver deterioration criteria^[3,4]; however, our concern is the presence of HCC in total liver, especially the tumor-occupying ratio ($GTV/TLV \times 100\%$). When this ratio exceeds 40% or 60%, TLV_{30Gy} then becomes greater than 40% or 60%, leading to the cutoff points being exceeded. Tumor occupying ratio was not found to be statistically significant in the present study (Table 2, $p=0.069$). Furthermore, the presence of Child B liver cirrhosis, as proposed by Liang *et al*^[1], and HBV, as proposed by Cheng *et al*^[2], as being risk factors for RILD were not statistically significant in the present study (Table 2, $p=0.086$ and $p=0.500$, respectively). Therefore, we consider that $FLV_{20Gy} \leq 20\%$, determined by calculating FL in NL, is a novel indicator for predicting RILD or CPS deterioration by 1.

A weakness of the present study is that we focused on HCCs associated with PVTT, so we cannot clarify whether it is valid to apply this predictive indicator of the risk of RILD to HCCs without

PVTT. Another limitation is that FL is based on the visual qualitative analysis. As Sawamura *et al.*^[9] proposed the quantitative analysis on GSA receptor activity, the quantitative analysis might be possible for 3DCRT. However, NL for 3DCRT was divided into four compartments: FL, dys-FL, radiation induced dys-FL and remaining FL. The RI accumulation degree for those compartments should be quantitatively analyzed and then, unified. It implies the complicated and difficult process for quantitative analysis. Our study proposed the mere succinct result of the initial qualitative analysis and the future quantitative analysis is warranted. Further, the common limitations exist in the study of Kim *et al.*^[4] and the present study on multivariate analysis: the number of event is limited compared with the variables (variables/events, 14/13 in the study of Kim *et al.*^[4] and 12/15 in the present study); positive correlated tendency existed among variables (correlation ratio width 0.614 to 0.967 in the study of Kim *et al.*^[4] and 0.689 to 0.899 in the present study. The presence of the common limitations implies that the obtained results should be recognized as the referring value with bias but not the determinant value without the bias. The result of $TLV_{30Gy} < 60\%$ obtained by Kim *et al.*^[4] could state that the liver volume destructed by HCC and RT should be repressed until 60% or less of total liver volume, and the result of $FLV_{20Gy} \leq 20\%$ obtained by the present study could state that the destructed volume by RT should separate from the destructed volume by HCC and should be repressed until 20% or less. The bias extent of the study by Kim *et al.* was unknown, whereas that of the present study was localized until less than FLV_{25Gy} or FLV_{30Gy} because we obtained the border between the 20 and 30 Gy iso-dose curve on every SPECT slice between radiation-induced dys-FL and remaining FL.

In conclusion, the present study evaluated the clinical parameters and dose volumetric parameters associated with RILD or CPS deterioration by 1 in HCC patients with PVTT treated by SPECT-B3DCRT. Univariate analysis revealed the association of all 12 dose-volumetric parameters with a risk of RILD or CPS deterioration by 1; these parameters correlated closely with each other, but no correlation was found among the clinical parameters. Multivariate analysis revealed only FLV_{20Gy} as having an association with the risk of RILD or CPS deterioration. $FLV_{20Gy} \leq 20\%$ appears to be a predictive indicator for avoiding the risk of RILD or CPS deterioration by 1.

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