의학석사 학위논문

Risk Factor Evaluation for Hepatic Decompensation after Stereotactic Body Radiation Therapy in Patients with Hepatocellular Carcinoma

간세포암종 환자에서 체부정위방사선치료 후
발생하는 간 대상부전 위험 인자 평가

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이 논문을 의학석사 학위 논문으로 제출함

2024 년 2 월

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양은영의 의학석사학위 논문을 인준함

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Abstract

Purpose: We examined the risk factors for patients with hepatocellular carcinoma (HCC) with underlying liver cirrhosis after undergoing stereotactic body radiation therapy (SBRT) with the primary endpoint of hepatic decompensation event.

Materials and Methods: This retrospective study reviewed the patients who underwent SBRT for HCC at Asan Medical Center from 2007 to 2017. Patients with a disease-free period of >2 years without history of decompensation event prior to SBRT were included. The patients were delivered a total dose of median 45 Gy in 3 fractions over consecutive days. Logistic regression was applied to patients' clinical and dosimetric factors for multivariate analysis, and the final model was evaluated through receiver operating characteristic (ROC) curve.

Results: The data of 138 patients were analyzed (median follow-up, 48.8 months; median age, 63 years; male sex, 76%; hepatitis B viral [HBV] etiology, 72%). Hepatic decompensation events occurred in 14 (10.1%) patients during the follow-up period. Patients were divided into the compensated and decompensated groups according to the occurrence of hepatic decompensation. In the compensated group, there were 25 women (20%) and 94 patients with HBV-associated cirrhosis (76%), whereas there were eight women (57%) and

six patients with HBV (43%) in the decompensated group (p=0.005 and 0.022, respectively). There was a significant difference in the baseline platelet count and prothrombin time ($p<0.05$). The multivariate analysis revealed that sex, HBV status, platelet count, and $V_{15\ Gy}$ (normal liver volume irradiated with $\geq$ 15 Gy) were associated with decompensation event risk. The model exhibited a balanced goodness of fit, moderate discrimination, and an area under the curve of 0.8629 in ROC curve analysis, indicating its potential for predicting hepatic decompensation event risk.

Conclusion: In conclusion, sex, etiology of liver cirrhosis, baseline platelet count, and $V_{15\ Gy}$ affected the occurrence of long-term hepatic decompensation event after SBRT in patients with HCC. These findings may help us establish the individualized dose constraints for each patient.

Keywords: hepatocellular carcinoma, stereotactic body radiation therapy, hepatic decompensation.

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Introduction

In 2018, primary liver cancer was the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide, whereas it was the second leading cause of cancer death in Republic of Korea [1, 2]. Moreover , hepatocellular carcinoma (HCC) accounts for 75–85% of primary liver cancer cases [1, 3]. It is characterized by high mortality rates as it is mostly detected at an advanced stage. Additionally, chronic liver disease in patients with HCC limits treatment options owing to decreased liver function and can be lethal [4, 5].

Although the tumor-node-metastasis classification is often used in other solid tumors, in HCC, various staging systems have been adopted, such as the Barcelona Clinic Liver Cancer (BCLC) system and modified Union for International Cancer Control system [5-8]. The BCLC staging system, which is commonly adopted by the European Association for the Study of the Liver, European Society for Medical Oncology, and American Association for the Study of the Liver guidelines, assesses liver function and reflects it in selecting treatment strategies. For patients with localized HCC with preserved liver function, curative treatment options, such as hepatic resection, liver transplantation (LT), or radiofrequency ablation (RFA) can be performed [5-9].

Hepatic resection is the best treatment option for patients with one or two small HCCs without underlying cirrhosis. The 5-year recurrence rate after hepatic resection is reportedly 40–80% [10, 11]. However, hepatic resection is possible for 20–30% of patients owing to

the limitation of the remaining functional liver volume and surgical morbidities [11].

LT can be administered to patients with HCC meeting the Milan criteria (single tumor ≤5 cm or small multinodular tumor [three nodules ≤3 cm]) even with fulminant liver failure [12]. LT for patients meeting the Milan criteria showed recurrence rates of 8–20% [13]. However, LT also has limitations, including a shortage of donors, ethical issues owing to surgical risks to healthy donors, and the need to take immunosuppressants for the whole life postoperatively.

RFA can be performed on patients who have three or fewer tumors ≤ 3 cm in size with high tumor control rate of 85–95%, if the hepatic resection is infeasible [14, 15]. RFA cannot be performed in tumors, which are located to the liver capsule, blood vessels, or central bile duct [16, 17]. The 5-year recurrence rate of RFA was reported to be 73.1% in a single institution retrospective study conducted in Republic of Korea [14].

Stereotactic body radiation therapy (SBRT) is an external beam radiation therapy that requires advanced techniques to deliver large ablative doses precisely in a small number of fractions [18]. With the rapid development of radiation treatment technologies, such as image-guided radiotherapy and intensity-modulated radiotherapy, it has become possible to perform SBRT with increased accuracy for small HCCs that are not candidates to hepatic resection, LT, or RFA. Although SBRT for small HCCs (≤3 cm in size) has been reported to have a high tumor control rate of >90% at 3 years [19, 20], treatment-induced long-term hepatic toxicity is not clearly understood. Without cancer progression, hepatic deterioration

alone can be fatal even after a long-term period. Therefore, a more in-depth study on radiation-induced hepatic toxicity is crucial.

Studies on liver function decline after SBRT have been conducted with endpoints of radiation-induced liver disease (RILD), Child–Pugh (CP) score elevation, and Albumin–Bilirubin grade elevation [21-25]. RILD is separated into the classic and non-classic types [26]. Classic RILD presents with hepatomegaly, ascites, thrombocytopenia, and alkaline phosphatase elevations within 3 months after liver irradiation mainly in patients without an underlying liver disease. This has been reported as conventional fractionation of the whole liver was performed for hepatic metastasis [27]. In contrast, the non-classic RILD is associated with partial liver irradiation in patients with HCC who have an underlying liver disease. Non-classic RILD presents with elevated serum transaminases >5 times of the upper limit of normal range, decrease in liver function as worsening of CP score by ≥2 points, and jaundice or reactivation of viral hepatitis within 3 months after radiotherapy [28]. Prior studies have shown that the Child–Pugh status prior to radiotherapy and the normal liver volume receiving ≥15 Gy are predictive factors for non-classic RILD [21-24, 29]. However, there is still a lack of consistent parameters that can provide concrete criteria for SBRT.

After SBRT, the occurrence of RILD is relatively less frequent compared to that after conventional radiation therapy. Furthermore, even if it does manifest, it tends to naturally resolve, thereby minimizing its clinical significance in real world practice [30, 31].

Conversely, hepatic decompensation, as observed in patients with end-stage liver cirrhosis,

manifests with refractory ascites, esophageal varix bleeding, hepatic encephalopathy, and spontaneous bacterial peritonitis, which is strongly associated with increased mortality rates attributed to liver failure [32, 33]. Consequently, it is necessary to assess hepatic decompensation events as a measure of liver toxicity following SBRT instead of RILD in patients with HCC with underlying liver conditions, such as cirrhosis. Nonetheless, to observe hepatic decompensation events, it is imperative to continuously monitor liver function over an extended duration while ensuring that there is no progression of HCC. Owing to the substantial challenges in recruiting eligible patients, no studies addressing this specific subject have been conducted to date.

Therefore, in this work, we aimed to evaluate the risk factor for long-term hepatic decompensation after SBRT to patients with HCC with underlying liver cirrhosis. The analysis included clinical and dosimetric factors, and we found the most relevant dosimetric factors to suggest dose constraints to control the risk of hepatic decompensation.

Materials and Methods

1) Study design

This is a retrospective study that reviewed medical records, including radiation treatment plans, of patients who underwent SBRT for HCC at Asan Medical Center from January 2007 to December 2017. The study protocol received approval from the Institutional Review Board (IRB) of Asan Medical Center (approval number: 2020-1933). The need to obtain written informed consent was waived owing to the retrospective nature of the study design.

2) Patients (Cohorts)

Patients aged ≥20 years with underlying liver cirrhosis and preserved hepatic function who received SBRT for HCC were included.

To determine whether SBRT causes long-term decompensation by causing toxicity in the normal liver tissue (total liver minus HCC), the patients included in the analysis were required to have preserved baseline liver function. Therefore, patients who had already undergone a decompensation event or experienced rapid deterioration within 3 months after the completion of SBRT were excluded from the analysis. Additionally, to prevent data contamination from liver function deterioration owing to HCC recurrence or additional anti-cancer treatment, we also excluded patients who relapsed within 2 years after SBRT or those

who received an additional treatment after SBRT.

3) Radiotherapy

For patients without surgical clips or compact iodized oil remaining after previous treatments, as well as for cases with HCC distant from the hepatic dome, three gold seeds (Standard Gold Soft Tissue Markers, CIVCO Medical Solutions, Kalona, IA, USA) were considered to be implanted into the liver parenchyma around the tumors under sonographic guidance as the fiducial markers, prior to computed tomography (CT) simulation. For patients without fiducial markers, image guidance using surgical clips, compact iodized oil, or hepatic dome was performed.

All patients were immobilized in the supine, arm-up position using a pillow and a vacuum mold. Free-breathing four-dimensional (4D) CT scanning was performed using a 16-slice CT system (GE LightSpeed RT 16; GE Healthcare, Waukesha, WI, USA), and all CT datasets were sorted into 10-phase bins that corresponded to the respiratory phase, using 4D imaging software (Advantage 4D; GE Healthcare). Using 4D CT scanning, amplitude-gated dose delivery was performed.

The gross tumor volume (GTV) was delineated based on the gross tumors observed on the CT simulation images at the end-expiratory phase, including tumors observed in liver dynamic CT or magnetic resonance imaging findings; the clinical target volume was the same as the GTV and extension to include movement within the gating phase (mostly 30–

70% phase) from the GTV was delineated as the internal target volume (ITV). The planning target volume (PTV) was expanded by 5 mm in all directions from the ITV.

SBRT planning employed a Varian Eclipse radiotherapy planning system which used multiple static conformal beams with 6-MV or 15-MV photons or volumetric modulated arc therapy (VMAT) technique using a 10-MV flattening filter-free beam with a maximum dose rate of 2400 MU/min. In VMAT plan, two semicircular-arc beams were used.

A dose of 12–20 Gy (median, 15 Gy) per fraction was given over 3–4 consecutive days to deliver a total dose of 36–60 (median, 45) Gy to the isodose line. The isodose line covering the PTV was 85–90%, which was normalized to the center of the PTV. The total prescription dose was determined based on our guidelines, including the following: (1) the maximum dose allowed to 700 mL of normal liver was estimated to be 15 Gy in three fractions and (2) the mean dose administered to normal liver was <13 Gy in three fractions. The dose limitations to other critical organs were as follows: (1) 2 mL of the esophagus or large bowel had to be limited to a total dose of <21 Gy; (2) 2 mL of the stomach or duodenum had to be limited to a total dose of <18 Gy; and (3) 2 mL of the spinal cord had to be limited to a total dose of 18 Gy.

Image guidance was performed before delivering each fraction of treatment using On-Board Imager (Varian Medical Systems) using cone-beam CT and gated fluoroscopy in the anterior-posterior and lateral directions.

4) Evaluation and follow-up

Patients' demographic data, laboratory data, and liver dynamic CT prior to SBRT were collected. After completion of SBRT, patients were examined every 2–3 months to check treatment response, recurrence, and adverse events. Laboratory tests, including complete blood count, biochemical profiles, coagulation tests, and/or imaging studies, were performed at each follow-up examination. A first event of hepatic decompensation, including refractory ascites, esophageal varix bleeding, hepatic encephalopathy, and spontaneous bacterial peritonitis, was established as the primary outcome considering its clinical significance. Follow-up was censored at the relapse of HCC, LT, or death without any events of hepatic decompensation.

5) Descriptive statistics

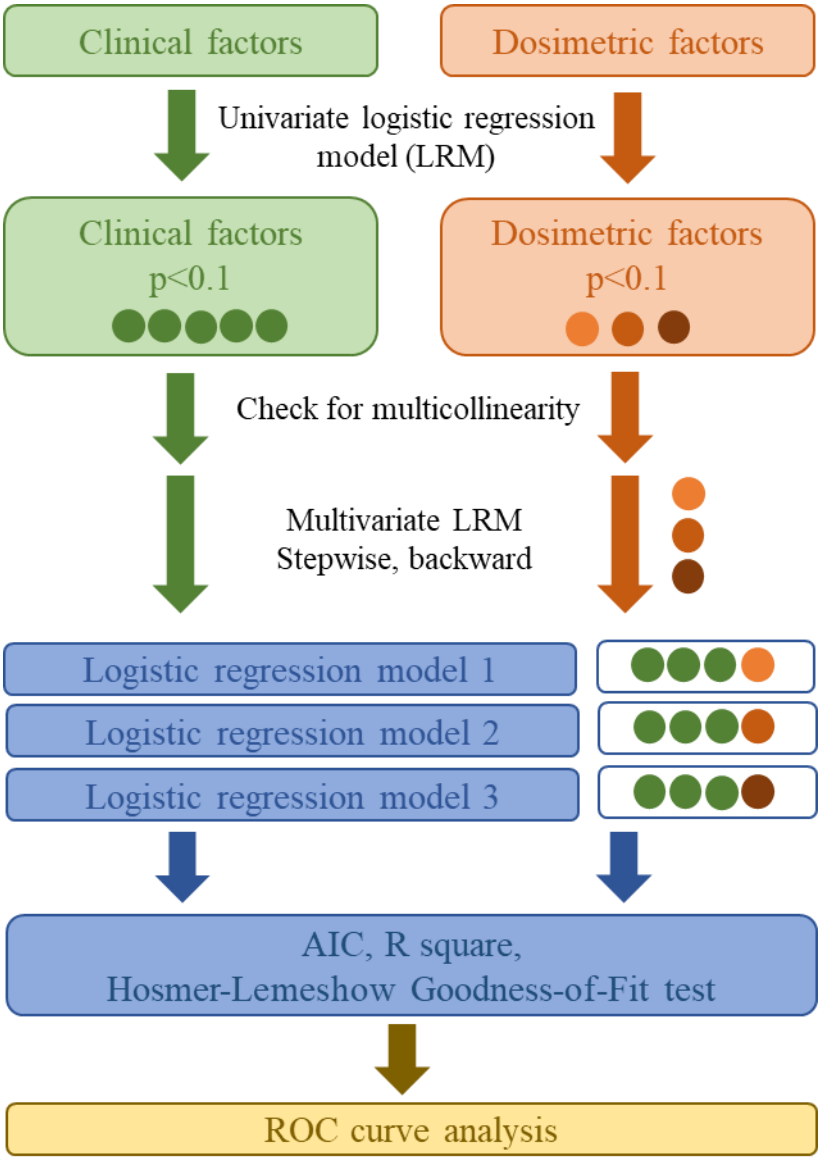
The total patient population was divided into patients with and those without hepatic decompensation, and analyzed in two ways. For patients' and treatment characteristics, Fisher's exact and Pearson's chi-square tests were used to analyze whether clinical and dosimetric factors were associated with the development of hepatic decompensation. As one of the dosimetric factors, we calculated the $V_{x\,Gy}$ at 5-Gy intervals from $V_{5\,Gy}$ to $V_{45\,Gy}$, where $V_{x\,Gy}$ represents the volume of the normal liver administered to over x Gy. In addition, $rV_{x\,Gy}$ indicates the volume of the normal liver receiving less than x Gy.

6) Risk factor evaluation for hepatic decompensation event

The univariate and multivariate logistic regression model was applied for the analysis of predictive factor for hepatic decompensation event and the process was depicted in Fig 1. First, univariate logistic regression analysis was performed to each clinical and dosimetric factors to investigate which factors were significantly associated with the occurrence of hepatic decompensation. Factors with a p-value <0.1 in the univariate analysis were included in the multivariate analysis, and whether there was multicollinearity among these factors was checked prior to the multivariate analysis. The multicollinearity with a variance inflation factor of ≥10 was confirmed among the dosimetric factors. Therefore, including all clinical factors with $p<0.1$ in the univariate analysis and each one of the dosimetric factors with $p<0.1$ in the univariate analysis at a time, ultimately three multivariate logistic regression analyses were conducted and three models were derived. For the models, we obtained the odds ratios (ORs) and β-constant values in the logistic regression analysis. This β-constant value was adopted to generate a formula to calculate the risk of the hepatic decompensation event. Each model was evaluated with the Akaike information criterion (AIC) [34], Tjur's R^2 [35], Nagelkerke's R^2 [36] and Hosmer–Lemeshow Goodness-of-Fit test [37]. The AIC is an estimator of prediction error and relative quality of statistical models for a given set of data, R-squared values calculate the coefficient of discrimination, and the Hosmer–Lemeshow Goodness-of-Fit test measures the fitness of the logistic model. Additionally, a receiver operating characteristic (ROC) curve analysis was performed to

evaluate the formula. All statistical analyses were performed using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Figure 1. Statistical analysis



AIC, Akaike information criterion; ROC, receiver operating characteristic

Results

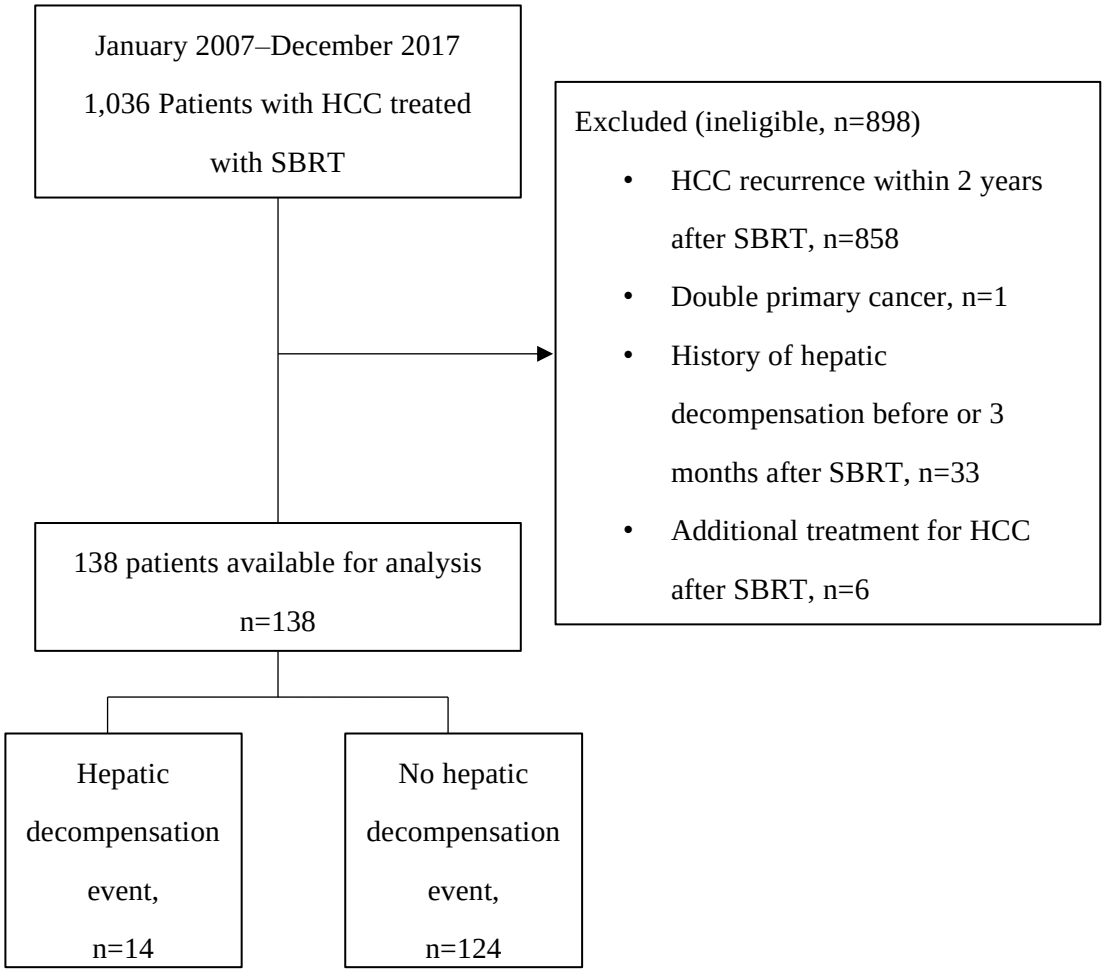
1) Patient and disease characteristics

In total, 138 patients were included in the analysis with a median follow-up period of 48.8 months (Fig 2). The patients' demographics and laboratory data are presented in Table 1. The median age of the patients was 63 (interquartile range [IQR], 57–69) years, and patients were predominantly male (n=105, 76%) and had hepatitis B viral (HBV) etiology (n=100, 72%). Moreover, 122 (88%) patients were of CP class A and the median platelet count was $104\times10^3/\mu L$ (IQR, 76–$139\times10^3/\mu L$). The median baseline liver volume was 11.07 (IQR, 9.50–12.65) dL. Finally, 14 patients (10.1%) developed a hepatic decompensation event during the follow-up period: especially, nine (64.3%), two (14.3%), two (14.3%), and one (7.1%) developed refractory ascites, variceal bleeding, hepatic encephalopathy, and spontaneous bacterial peritonitis, respectively.

When patients were grouped according to the occurrence of hepatic decompensation, there were 25 women (20%) and 94 patients with HBV-associated cirrhosis (76%) in the compensated group, whereas there were eight women (57%) and six patients with HBV (43%) in the decompensated group (p=0.005 and 0.022, respectively). The median platelet count and prothrombin time were $107\times10^3/\mu L$ (IQR, 82–$144\times10^3/\mu L$), 1.07 INR (IQR, 1.01–1.14 INR) in the compensated group compared to $74\times10^3/\mu L$ (IQR, 67–$98\times10^3/\mu L$) and 1.16 INR (IQR, 1.06–1.19 INR) in the decompensated group, respectively (p=0.004 and 0.035,

respectively). Moreover, there were 111 (90%) and 11 patients (79%) with CP class A in the compensated and decompensated groups, respectively (p=0.2).

Figure 2. Patients flow chart



HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy

Table 1. Patient characteristics

Variables		Hepatic decompensation event		Total	p-value
		No (n=124)	Yes (n=14)	(n=138)	
Age, years		63 (56–69)	66 (60–71)	63 (57–69)	0.2
Sex (n, %)	Male	99 (80)	6 (43)	105 (76)	0.005
	Female	25 (20)	8 (57)	33 (24)	
Etiology of LC (n, %)	HBV	94 (76)	6 (43)	100 (72)	0.022
	Others	30 (24)	8 (57)	38 (28)	
Diabetes mellitus (n, %)		39 (31)	7 (50)	46 (33)	0.2
Hypertension (n, %)		49 (40)	8 (57)	57 (41)	0.2
Hemoglobin, mg/dL		13.7 (12.4–14.7)	12.1 (11.2–13.1)	13.6 (12.3–14.7)	0.008
Platelet, $\times 10^3/\mu L$		107 (82–144)	74 (67–98)	104 (76–139)	0.004
Prothrombin time, %		89 (77–97)	73 (70–89)	87 (75–97)	0.024
Prothrombin time, INR		1.07 (1.01–1.14)	1.16 (1.06–1.19)	1.07 (1.02–1.15)	0.035
Albumin, g/dL		3.9 (3.6–4.2)	3.7 (3.3–3.9)	3.9 (3.6–4.2)	0.062
AST, IU/L		31 (25–41)	37 (33–43)	33 (25–42)	0.13
ALT, IU/L		24 (16–34)	18 (14–27)	22 (16–34)	0.2
Total bilirubin, mg/dL		0.8 (0.6–1.0)	1.3 (0.9–1.7)	0.8 (0.6–1.1)	<0.001
Total cholesterol, mg/dL		151 (136–171)	144 (124–161)	151 (135–171)	0.2
Baseline liver volume, dL		11.10 (9.58–12.74)	10.84 (9.52–11.58)	11.07 (9.50–12.65)	0.5
Child–Pugh class (n, %)	A	111 (90)	11 (79)	122 (88)	0.2
	B	13 (10)	3 (21)	16 (12)	

ALT, Alanine aminotransferase; AST, aspartate aminotransaminase; HBV, hepatitis B virus; LC, liver cirrhosis

2) Radiotherapy and dosimetric parameters

In total, 117 (84.8%) patients were delivered 45 Gy in three fractions over 3 consecutive days following our standard protocol. SBRT regimen and dosimetric factors are described in Table 2. Patients without subsequent hepatic decompensation event had a lower median GTV of 0.03 (IQR, 0.02–0.06) dL compared to 0.06 (IQR, 0.04–0.08) dL in the decompensated group (p=0.031). However, there was no significant difference in the PTV, normal liver volume, mean liver dose, and from $V_{5\ Gy}$ to $V_{45\ Gy}$ between the two groups.

Table 2. Treatment & dosimetric characteristics according to the decompensation event

Variables		Hepatic decompensation event		Total (n=138)	p-value
		No (n=124)	Yes (n=14)		
SBRT regimen	36 Gy/3fx	7 (5.6)	2 (14.3)	9 (6.5)	
	45 Gy/3fx	106 (85.5)	11 (78.6)	117 (84.8)	
	48 Gy/3fx	1 (0.8)	0 (0.0)	1 (0.7)	
	60 Gy/4fx	8 (6.5)	1 (7.1)	9 (6.5)	
	60 Gy/3fx	2 (1.6)	0 (0.0)	2 (1.5)	
GTV, dL		0.03 (0.02–0.06)	0.06 (0.04–0.08)	0.04 (0.02–0.06)	0.031
PTV, dL		0.23 (0.16–0.32)	0.26 (0.21–0.38)	0.23 (0.16–0.34)	0.2
Normal liver volume, dL		11.94 (9.96–13.51)	11.28 (10.09–12.69)	11.87 (9.99–13.48)	0.7
Mean liver dose, Gy		5.25 (4.17–6.96)	5.86 (5.01–8.89)	5.33 (4.32–6.98)	0.2
$V_{5\ Gy}$, dL		3.48 (2.63–4.58)	3.59 (2.40–6.20)	3.48 (2.62–4.70)	0.5
$V_{10\ Gy}$, dL		1.88 (1.47–2.60)	2.11 (1.54–4.06)	1.88 (1.48–2.65)	0.4
$V_{15\ Gy}$, dL		1.12 (0.84–1.43)	1.18 (0.92–2.76)	1.12 (0.85–1.49)	0.3
$V_{20\ Gy}$, dL		0.70 (0.50–0.92)	0.84 (0.56–1.67)	0.71 (0.51–0.93)	0.3
$V_{25\ Gy}$, dL		0.48 (0.35–0.64)	0.58 (0.37–1.07)	0.48 (0.35–0.65)	0.3
$V_{30\ Gy}$, dL		0.36 (0.26–0.48)	0.43 (0.27–0.77)	0.36 (0.26–0.49)	0.3
$V_{35\ Gy}$, dL		0.28 (0.20–0.37)	0.34 (0.20–0.60)	0.28 (0.20–0.37)	0.4
$V_{40\ Gy}$, dL		0.21 (0.14–0.29)	0.23 (0.13–0.42)	0.22 (0.14–0.29)	0.6
$V_{45\ Gy}$, dL		0.15 (0.10–0.20)	0.16 (0.07–0.31)	0.15 (0.10–0.21)	0.9
$rV_{5\ Gy}$, dL		8.00 (6.29–9.74)	6.71 (6.01–7.80)	7.88 (6.19–9.65)	0.13
$rV_{10\ Gy}$, dL		9.74 (7.92–11.26)	8.48 (7.44–9.62)	9.57 (7.90–11.23)	0.14
$rV_{15\ Gy}$, dL		10.53 (8.64–12.19)	9.26 (8.31–10.95)	10.50 (8.64–12.09)	0.2
$rV_{20\ Gy}$, dL		11.01 (9.09–12.68)	10.00 (9.28–11.42)	10.78 (9.11–12.61)	0.4

$rV_{25\ Gy}$, dL	11.17 (9.36–12.93)	10.48 (9.48–11.69)	11.07 (9.38–12.90)	0.5
$rV_{30\ Gy}$, dL	11.24 (9.51–13.08)	10.72 (9.62–11.86)	11.21 (9.54–13.04)	0.5
$rV_{35\ Gy}$, dL	11.30 (9.60–13.17)	10.85 (9.69–11.99)	11.30 (9.62–13.13)	0.6
$rV_{40\ Gy}$, dL	11.38 (9.79–13.23)	10.94 (9.75–12.47)	11.38 (9.75–13.19)	0.7
$rV_{45\ Gy}$, dL	11.46 (9.82–13.30)	11.01 (9.82–12.66)	11.46 (9.81–13.24)	0.7

GTV, gross tumor volume; PTV, planning target volume; SBRT, stereotactic body radiation therapy

3) Prognostic factors associated with hepatic decompensation

Applying the univariate logistic regression analysis including clinical and dosimetric factors, we analyzed the association between factors and decompensation event again as shown in Tables 3–4. Among the clinical factors, sex, etiology of liver cirrhosis, hemoglobin, platelet count, prothrombin time, and albumin had a p-value <0.1 in the univariate logistic regression without multicollinearity, and $V_{10\ Gy}$, $V_{15\ Gy}$, and $V_{20\ Gy}$ had a p-value <0.1 among dosimetric factors with multicollinearity. Multivariate analysis with logistic regression model and backward method of stepwise was applied to clinical factors and each one of dosimetric factors considering multicollinearity. In each multivariate analysis, three clinical factors of sex, etiology of LC, platelet count, and all the dosimetric factors were found to be appropriate to establish the model to calculate the risk of hepatic decompensation. The OR and β-constant values of each factor in multivariate logistic regression analysis are listed in Table 5.

Table 3. Univariate logistic regression analysis of clinical factors associated with hepatic decompensation

Variables (reference)	Univariate analysis	
	OR (95% CI)	p-value
Clinical factors		
Age	1.04 (0.98–1.11)	0.2
Sex (Male)	5.28 (1.69–17.4)	0.004
Etiology of LC (HBV)	4.18 (1.35–13.6)	0.014
Diabetes mellitus (No)	2.18 (0.70–6.78)	0.2
Hypertension (No)	2.04 (0.67–6.54)	0.2
Hemoglobin, mg/dL	0.66 (0.47–0.90)	0.011
Platelet, $\times 10^3/\mu L$	0.98 (0.96–0.99)	0.012
Prothrombin time, %	0.97 (0.95–1.00)	0.084
Albumin, g/dL	0.30 (0.10–0.91)	0.032
AST, IU/L	1.01 (0.97–1.04)	0.6
ALT, IU/L	0.97 (0.91–1.01)	0.2
Total bilirubin, mg/dL	1.30 (0.81–2.15)	0.2
Total cholesterol, mg/dL	1.52 (0.82–2.62)	0.15
Child–Pugh class (A)	2.33 (0.48–8.68)	0.2
Baseline liver volume, dL	0.94 (0.73–1.18)	0.6

ALT, alanine aminotransferase; AST, aspartate aminotransaminase; CI, confidence interval; HBV, hepatitis B virus; LC, liver cirrhosis; OR, odds ratio

Table 4. Univariate logistic regression analysis of dosimetric factors associated with hepatic decompensation

Variables (reference)	Univariate analysis	
	OR (95% CI)	p-value
Dosimetric factors		
$BED_{10\ Gy}$	0.98 (0.94–1.02)	0.4
Gross tumor volume, dL	1.97 (0.01–37.9)	0.7
Planning target volume, dL	1.35 (0.18–4.91)	0.7
Mean liver dose		0.9
$V_{5\ Gy}$, dL	1.26 (0.91–1.72)	0.15
$V_{10\ Gy}$, dL	1.45 (0.98–2.11)	0.052
$V_{15\ Gy}$, dL	1.77 (0.99–3.08)	0.043
$V_{20\ Gy}$, dL	2.08 (0.85–4.73)	0.083
$V_{25\ Gy}$, dL	2.35 (0.70–7.04)	0.13
$V_{30\ Gy}$, dL	2.53 (0.55–9.87)	0.2
$V_{35\ Gy}$, dL	2.65 (0.39–14.0)	0.2
$V_{40\ Gy}$, dL	1.79 (0.11–13.2)	0.6
$V_{45\ Gy}$, dL	1.27 (0.02–14.5)	0.9
$rV_{5\ Gy}$, dL	0.89 (0.70–1.10)	0.3
$rV_{10\ Gy}$, dL	0.88 (0.68–1.10)	0.3
$rV_{15\ Gy}$, dL	0.91 (0.70–1.14)	0.4
$rV_{20\ Gy}$, dL	0.94 (0.73–1.19)	0.6
$rV_{25\ Gy}$, dL	0.96 (0.74–1.21)	0.7
$rV_{30\ Gy}$, dL	0.96 (0.75–1.22)	0.8
$rV_{35\ Gy}$, dL	0.97 (0.76–1.23)	0.8
$rV_{40\ Gy}$, dL	0.98 (0.76–1.24)	0.9
$rV_{45\ Gy}$, dL	0.99 (0.77–1.25)	>0.9

BED, biologically effective dose; CI, confidence interval; OR, odds ratio

Table 5. Multivariate logistic regression analysis of clinical and dosimetric factors associated with hepatic decompensation

Table 5-1. Multivariate analysis with $V_{10\ Gy}$

Variables (reference)	Multivariate analysis		
	B	OR (95% CI)	*p*-value
Sex (Male)	1.909	6.75 (1.67–27.30)	0.007
Etiology of LC (HBV)	1.292	3.64 (0.97–13.62)	0.055
Platelet, $\times 10^3/\mu L$	-0.024	0.98 (0.96–1.00)	0.019
$V_{10\ Gy}$, dL	0.492	1.64 (1.00–2.69)	0.052

AIC: 75.017, Tjur's R^2: 0.247, Nagelkerke's R^2: 0.352, p-value of Hosmer–Lemeshow Goodness-of-Fit test: 0.198

Table 5-2. Multivariate analysis with $V_{15\ Gy}$

Variables (reference)	Multivariate analysis		
	B	OR (95% CI)	*p*-value
Sex (Male)	1.921	6.83 (1.68–27.81)	0.007
Etiology of LC (HBV)	1.337	3.81 (1.03–14.05)	0.045
Platelet, $\times 10^3/\mu L$	-0.024	0.98 (0.96–1.00)	0.025
$V_{15\ Gy}$, dL	0.707	2.03 (1.00–4.12)	0.051

AIC: 75.135, Tjur's R^2: 0.242, Nagelkerke's R^2: 0.350, p-value of Hosmer–Lemeshow Goodness-of-Fit test: 0.205

Table 5-3. Multivariate analysis with $V_{20\ Gy}$

Variables (reference)	Multivariate analysis		
	B	OR (95% CI)	*p*-value
Sex (Male)	1.806	6.09 (1.56–23.77)	0.009
Etiology of LC (HBV)	1.455	4.28 (1.19–15.45)	0.026
Platelet, $\times 10^3/\mu L$	-0.024	0.98 (0.96–1.00)	0.024
$V_{20\ Gy}$, dL	0.870	2.39 (0.85–6.68)	0.097

AIC: 76.342, Tjur's R^2: 0.220, Nagelkerke's R^2: 0.335, p-value of Hosmer–Lemeshow Goodness-of-Fit test: 0.502

CI, confidence interval; LC, liver cirrhosis; HBV, hepatitis B virus; OR, odds ratio

4) Evaluation of risk of hepatic decompensation

Based on the multivariate logistic regression model, the risk of hepatic decompensation, p can be calculated using the following equations with $V_{15\ Gy}$ (Table 5-2):

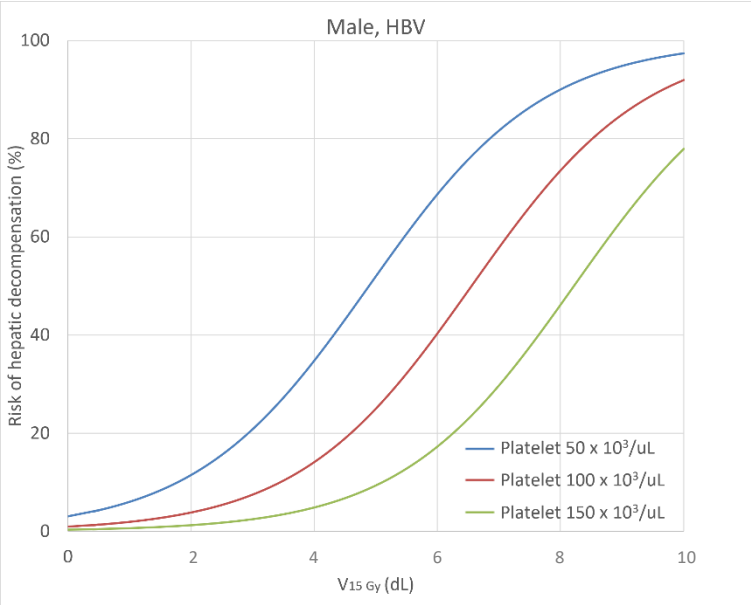
$$p = \frac{1}{1+e^{-S}},\ 0 \le p \le 1 \quad (1)$$

$$S = 1.921 \times \left(\begin{smallmatrix} 0: Male \\ 1: Female \end{smallmatrix}\right) + 1.337 \times \left(\begin{smallmatrix} 0: HBV \\ 1: non-HBV \end{smallmatrix}\right) - 0.024 \times Platelet(10^3/\mu L) +$$

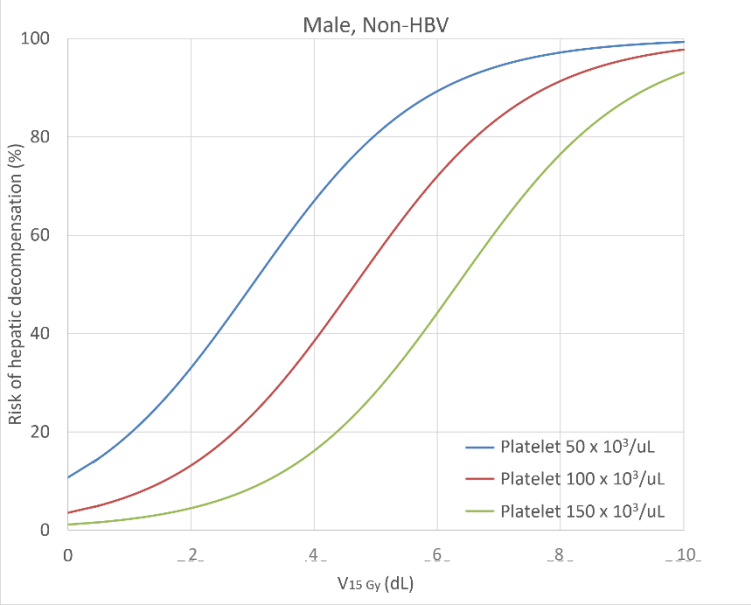
$$0.707 \times V_{15\ Gy}(dL) - 2.281 \quad (2)$$

The risk of hepatic decompensation according to $V_{15\ Gy}$ by platelet count for each sex and etiology of LC group is presented in Fig 3. When the model is evaluated, AIC value was 75.135, suggests that the model's goodness of fit and complexity are balanced [34]. Tjur's R^2 value was 0.242, indicating a moderate level of discrimination [35], the percentage of the correctly predicted value was 0.862, and Nagelkerke's R^2 was 0.350 [36]. In the Hosmer–Lemeshow Goodness-of-Fit test, the p-value was 0.205, suggesting that the model's goodness-of-fit is reasonable [37].

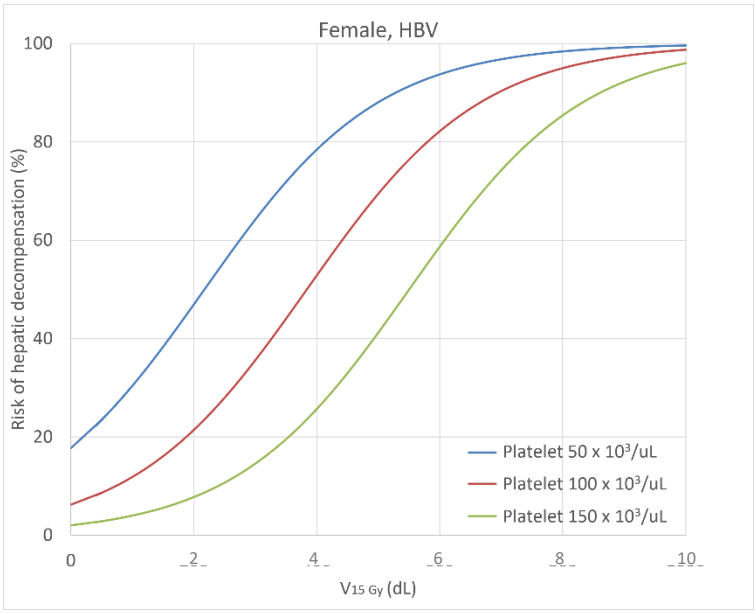
Figure 3. Hepatic decompensation risk curve, A) for male sex and HBV etiology, B) for male sex and non-HBV etiology, C) for female sex and HBV etiology, D) for female sex and non-HBV etiology



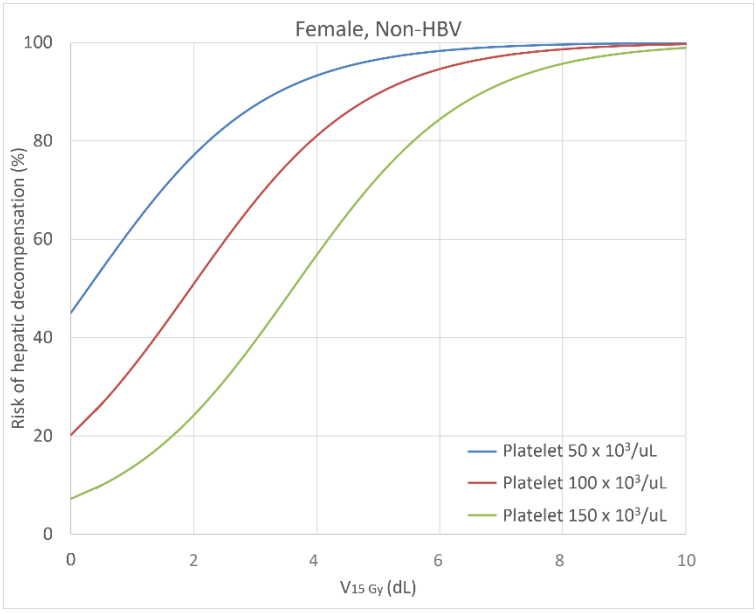
A)



B)


Female, HBV
Risk of hepatic decompensation (%)
100
80
60
40
20
0
0
2
4
6
8
10
V15 Gy (dL)
Platelet 50 x 10³/uL
Platelet 100 x 10³/uL
Platelet 150 x 10³/uL

C)

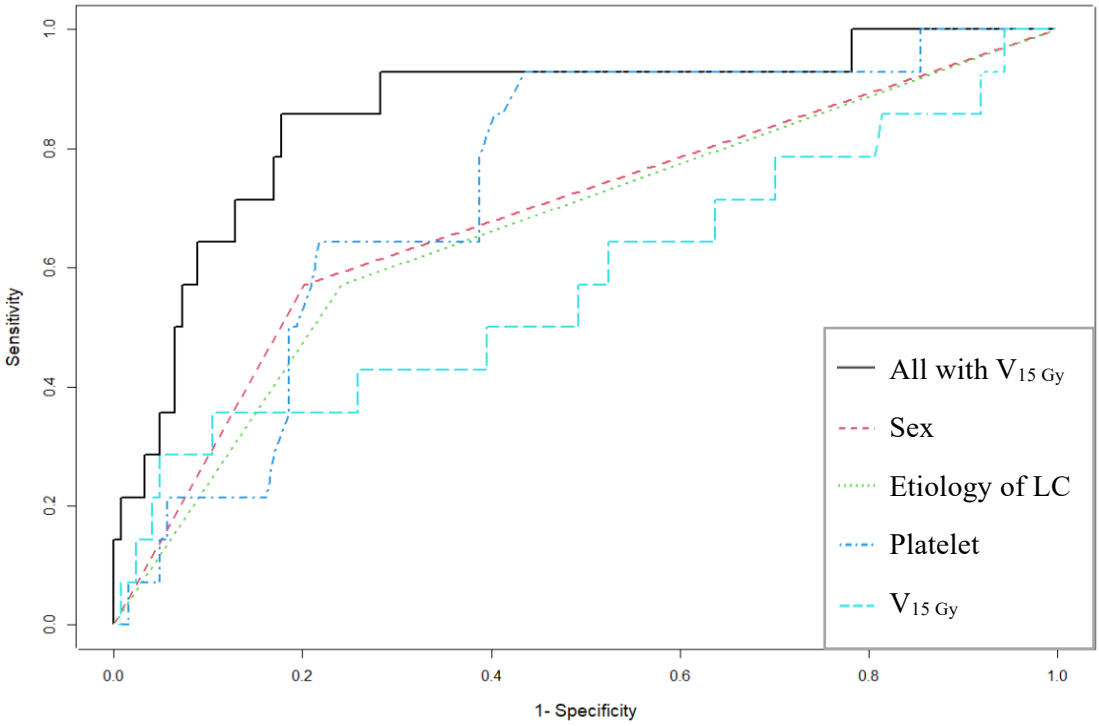

Female, Non-HBV
Risk of hepatic decompensation (%)
100
80
60
40
20
0
0
2
4
6
8
10
V15 Gy (dL)
Platelet 50 x 10³/uL
Platelet 100 x 10³/uL
Platelet 150 x 10³/uL

D)

5) ROC curve

We performed ROC curve analysis; the results are presented in Fig 4. Multivariate logistic regression model, including sex, etiology of LC, platelet count, and $V_{15\ Gy}$, showed an area under the curve (AUC) of 0.8629. With a threshold of 0.113, we obtained a median sensitivity of 0.8571 (95% CI, 0.6429–1) and a median specificity of 0.8226 (95% CI, 0.7581–0.8871).

Figure 4. ROC curve of each factor and multivariate logistic regression model for hepatic decompensation



AUC of All with $V_{15\ Gy}$: 0.863 (95% CI, 0.759–0.967), AUC of Sex: 0.685 (0.551–0.819), AUC of Etiology of LC: 0.665 (0.53–0.8), AUC of Platelet: 0.736 (0.615–0.857), AUC of $V_{15\ Gy}$: 0.578 (95% CI, 0.399–0.757)

AUC, area under the curve; LC, liver cirrhosis; ROC, receiver operating characteristic

6) Dose constraint for normal liver

For the treatment planning, it is necessary to determine the dose constraint of normal liver to confine the risk of developing hepatic decompensation after SBRT within a certain level. For this purpose, equations (1) and (2) can be transformed into (3) and (4) as follows and the dose constraint of normal liver can be described as a function of platelet count in a patient with specific sex and liver cirrhosis etiology.

$$S = \ln\left(\frac{p}{1-p}\right) \quad (3)$$

$$\mathrm{V}_{15\ \mathrm{Gy}}(dL) = \frac{1}{0.707}\left[\ln\left(\frac{p}{1-p}\right) - 1.921 \times \left(\begin{smallmatrix}\text{0: Male}\\ \text{1: Female}\end{smallmatrix}\right) - 1.337 \times \left(\begin{smallmatrix}\text{0: HBV}\\ \text{1: non-HBV}\end{smallmatrix}\right) + 0.024 \times \mathrm{Platelet}\ (10^3/\mu L) + 2.281\right] \quad (4)$$

For example, for the 5% an 15% risk of liver decompensation, $V_{15\ Gy}$ as a function of platelet count is shown in Fig 5. In the case of female, non-HBV, assuming the same platelet count, the $V_{15\ Gy}$ for the 15% risk of liver decompensation was lower than that in male sex patient with HBV-related liver cirrhosis.

Figure 5. Dose constraint as $V_{15\ Gy}$ according to the risk of hepatic decompensation

Figure 5-1. $V_{15\ Gy}$ with 5% risk of hepatic decompensation

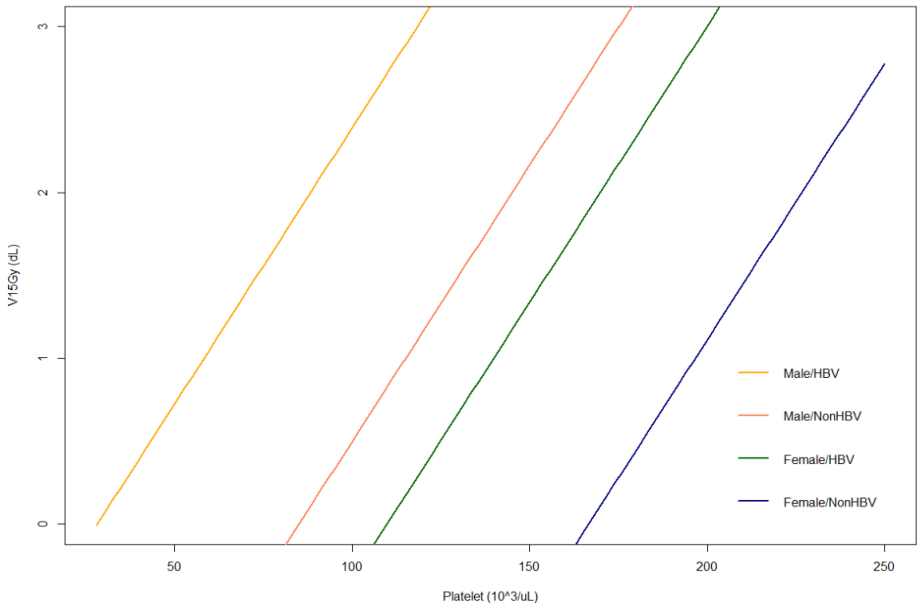
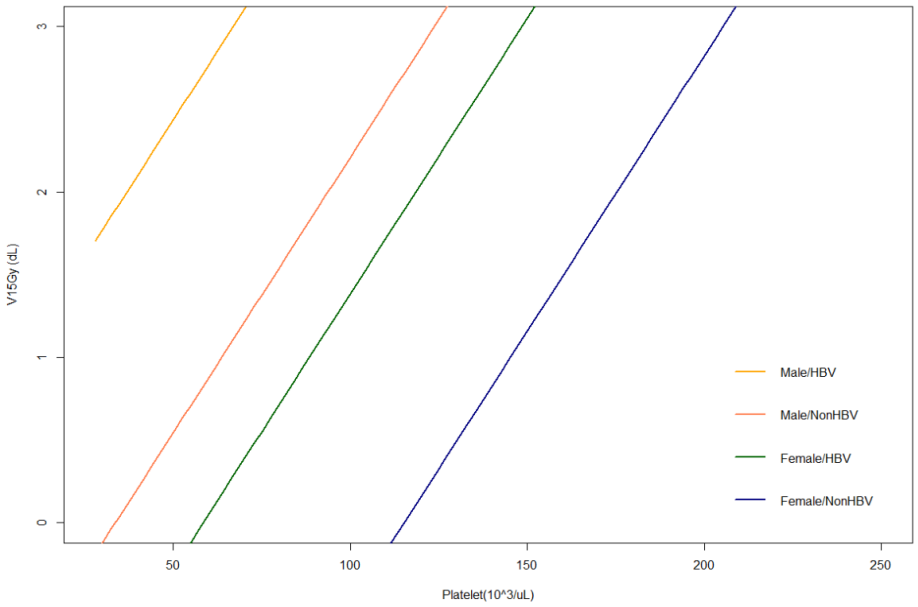


Figure 5-2. $V_{15\ Gy}$ with 15% risk of hepatic decompensation



Discussion

In this study, we analyzed the clinical and dosimetric data of 138 patients, including 14 patients who experienced hepatic decompensation after SBRT. Our findings demonstrated that a higher risk of hepatic decompensation after SBRT in patients with HCC was associated with female sex, non-HBV, lower platelet count, and larger $V_{15\ Gy}$ volume. When the above four factors were applied to the logistic regression model, the following formula could be derived using the beta constant value: Risk of hepatic decompensation = $\frac{1}{1+e^{-S}}$, $S = 1.921 \times \left(\begin{smallmatrix}0\text{: Male}\\1\text{: Female}\end{smallmatrix}\right) + 1.337 \times \left(\begin{smallmatrix}0\text{: HBV}\\1\text{: non-HBV}\end{smallmatrix}\right) - 0.024 \times \text{Platelet}(10^3/\mu L) + 0.707 \times V_{15\ Gy}(dL) - 2.281.$

To our knowledge, this is the first study to evaluate the risk factors for hepatic decompensation after SBRT in patients with HCC. In comparison to RILD, hepatic decompensation exhibits a robust association with hepatic failure. Thus, the findings of this study are important and represent a clinically significant indicator.

The most influential factor that was associated with decompensation events was female sex having an OR of 6.83 (95% CI: 1.68–27.81). Prior studies on HCC have typically demonstrated a less favorable prognosis among male patients compared to the corresponding of their female counterparts. According to a study by Lam et al that analyzed the influence of sex on survival after curative surgery or ablative therapy in HCC, the median survival of female was 25.7 months longer than that of male participants (p=0.012) [38]. Ng et al,

reported frequent encapsulation and lower tumor invasiveness through the surgical resection, which resulted in better survival rates in female patients [39]. In a previous phase II study at our institution, which reported the clinical outcomes following SBRT for HCC in patients not amenable to curative treatment, there was no significant difference in recurrence-free survival and overall survival rates according to sex (hazard ratio [HR] of male, 1.891; 95% CI, 0.733–4.876; p=0.188; HR of male 0.972; 95% CI 0.206–4.582; p=0.971, respectively) [20]. In a retrospective analysis conducted by Park et al, there was no significant difference in overall survival according to sex after SBRT for HCC [40]. However, as previous studies have primarily employed survival as their endpoint, often linked to frequent tumor progression, it is challenging to make direct comparisons with the findings of the present study. In our study, a distinct approach was taken by excluding patients who experienced recurrence within 2 years. This allowed for a focused evaluation of the long-term effects of SBRT, setting our findings apart from those of earlier research. Our result that female sex had a higher association with hepatic decompensation after SBRT suggested the possibility that female patients with HCC might be more vulnerable to radiotherapy and may require different dose constraints depending on sex.

The second influential factors were non-HBV etiology of LC having an OR of 3.81 (95% CI: 1.03–14.05) compared to HBV in multivariate analysis. These findings were in alignment with the outcomes observed in prior studies. Choi et al. conducted a study, in which they categorized patients with HCC treated at a single institution over a 16-year period

into three distinct cohorts: those treated in 2000–2004, 2005–2009, and 2010–2015. Their analysis aimed to explore the variations in patient characteristics and treatment outcomes across these time periods [41].

The proportion of HBV patients in each cohort was 76.6%, 74.4%, and 74.0%. However, the percentage of patients who received nucleotide analogue treatment increased gradually, measuring 8.6%, 25.5%, and 62.8% ($p<0.001$) across the three cohorts. Furthermore, when analyzing prognostic factors related to overall survival within each cohort, it was noted that, unlike the previous two groups, patients with HBV in the most recent cohort exhibited improved overall survival rates. These findings suggested that the preservation of liver function among patients with HBV owing to the use of nucleotide analogue treatment could have contributed to the improvement in the overall survival rate. Based on the outcomes of the prior study, we can speculate that the favorable hepatic function in patients with HBV in the present study can be attributed to the use of nucleotide analogue treatment.

Our study revealed that a lower platelet count prior to SBRT was associated with a higher risk of hepatic decompensation after SBRT. In a systematic review of 33 studies that aimed to analyze the association between the platelet count and survival in patients with HCC, the lower platelet count was found to be associated with a poor overall survival with a pooled HR of 1.41 (95% CI: 1.14–1.75) regardless of treatment modality for HCC [42]. Additionally, in another work thrombocytopenia occurred in >60% of patients with liver cirrhosis or fibrosis [43]. For the patients with chronic liver disease, thrombocytopenia may be caused

by decreased liver function resulting in decreased platelet production and increased sequestration and destruction [44]. Therefore, based on this biological viewpoint, it can be assumed that patients with thrombocytopenia are already suffering from decreased liver function, which may increase the possibility of decompensation even after SBRT.

Among dosimetric factors, we found that the high-dose bath of $V_{15\ Gy}$ was associated with the increased risk of hepatic decompensation after SBRT. As the previous studies have also shown that $V_{15\ Gy}$ in hypofractionated radiation therapy was associated with increased risk of non-classic RILD [21-23], we may conclude that $V_{15\ Gy}$ can affect short-term and long-term liver function decline. Though the β-constant value of $V_{15\ Gy}$ in our prediction model for decompensation event was as small as 0.707, it can be pivotal in the high-risk group. In the highest risk group (as seen in Fig 2D), which consists of female patients without HBV, the curve demonstrates that for the patients with a platelet count of 50,000/μL, when the $V_{15\ Gy}$ is 0 dL, the probability of a decompensation event is 45%, However, when the $V_{15\ Gy}$ increases to 1 dL, there is a 17% increase (up to 62%) in the probability to occur such an event. Conversely, among patients with a platelet count of 150,000/μL in the highest risk group, as the $V_{15\ Gy}$ increases from 0 to 1 dL, there is a 6% rise in the probability, going from 7% to 13%. Therefore, greater caution is needed to minimize high-dose areas and low-dose irradiation when developing a radiotherapy plan for the highest risk group of patients. However, normal liver volume irradiated with a low dose of <10–15 Gy also has been mentioned as an important factor in causing RILD [23, 25]. However, since our institution

already has a dose limit of $rV_{15\ Gy}$ to more than 700 mL, the importance of $rV_{15\ Gy}$ is not expected to be clearly revealed in this analysis [45].

The suggested model requires at least four pieces of information to assess the risk of hepatic decompensation. Although the four risk factors included in this equation were confirmed to have no multicollinearity, there are still doubts as to whether they act as confounding factors. Additionally, as a lot of information is required, it may be inconvenient when applied in practice. However, Naqa et al suggested the normal tissue complication probability model using dosimetric information, biological markers and imaging and found that the model including multiple factors predict the liver toxicity better than the model with only dosimetric factor [46]. In particular, the dosimetric factor can be adjusted differently in contrast to the etiology of cirrhosis and sex, which can make radiotherapy safer.

The high local control of SBRT in small HCC has been established in previous studies, and its use is gradually expanding [20, 40, 47-53] for large HCCs, which is not amenable for the other treatment strategy. Therefore, preserving hepatic function of normal liver by reducing the $V_{15\ Gy}$ and higher dose delivery to the tumor could be a key factor in determining the prognosis after SBRT. To irradiate the higher dose safely, particle treatment that shows lower split of radiation considering the Bragg peak can be a method. In a prospective study, Shibuya et al, reported that grade 3 acute and late toxicities, and no grade 4 or 5 adverse events, were observed in two patients after providing a C-ion radiotherapy dose of 52.8 Gy in four fractions to HCCs $\leq$10 cm in size [54]. For proton therapy, Bush et al also reported

that there was no significant change in hepatic function after a 6-month proton therapy with 63 Gy over 3 weeks to an HCC with a median size of 5.5 cm [55]. In the future, the optimization of radiotherapy for HCC, which includes the cutting-edge techniques, such as particle therapy, is necessary, and more results should be accumulated.

This study had several limitations because of its retrospective nature. First, the number of patients included in the analysis was small as we excluded the patients who had recurrence within 2 years after SBRT. However, we could exactly rule out that the cause of hepatic decompensation following SBRT is disease progression in this criterion. A multi-center study is needed to secure greater statistical significance and confirm our results. Second, a prediction model validation was not performed. In this study, we tried to show the validity of the model by using the ROC curve instead, but external validation of the model would be necessary in the future for more accurate verification.

Conclusion

We evaluated the risk factors for long-term hepatic decompensation after SBRT for patients with HCC with underlying liver cirrhosis. The multivariate analysis showed that sex, etiology of liver cirrhosis, baseline platelet count, and $V_{15\ Gy}$ for normal liver affected the occurrence of hepatic decompensation event. It is imperative to establish individualized SBRT dose constraints that are specifically tailored to each patient's hepatic function to perform safer SBRT.

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국문요약

목적: 우리는 기저 간 경변증이 있는 간세포암종 환자에서 체부정위방사선치료 후 장기적인 간 대상부전 사건 발생위험에 대한 위험을 예측할 수 있는 인자를 평가하는 것을 목표로 하였다.

대상 및 방법: 본 연구는 후향적 연구로 2007 년부터 2017 년까지 서울아산병원에서 간세포암종에 대해 체부정위방사선치료를 시행한 환자들을 대상으로 하였다. 방사선치료 이전에 간 대상부전의 병력 없이 2 년 이상의 무병생존기간을 보인 환자들이 포함되었다. 방사선치료는 중앙값 45 Gy 의 총 선량을 3 일 동안 조사하였다. 다변량 분석을 위해 환자의 임상적 요인과 선량계측 요인에 로지스틱 회귀분석을 적용하였고, ROC 곡선을 통해 모델을 평가하였다.

결과: 이 연구에는 총 138 명의 환자들이 분석에 포함되었으며 평균 추적 기간은 48.8 개월이었다. 환자들의 중앙연령은 63 세였으며, 대부분 남성 (76%), B 형 간염 바이러스 병인 (72%)이 포함되었다. 추적 기간 동안 환자의 10.1%에서 간 대상부전이 발생하였다. 간 대상부전의 발생 여부에 따라 대상부전군과 비대상부전군으로 환자를 분류하였다. 비대상부전 집단에서는 HBV 관련 간경변증 환자가 25 명(20%), HBV 관련 간경변증 환자는 94 명(76%)인 반면 대상부전 집단에서는 8 명의 여성(57%)과 6 명의 HBV 환자(43%)가 포함되었다(각각 p=0.005, 0.022). 두 집단의 치료 전 기준 혈소판 수

와 프로트롬빈 시간에는 유의한 차이가 있었다. 다변량 로지스틱 모델을 통해 대상부전 사건 위험과 관련된 요인을 분석하여 성별, 간경변의 병인(HBV 여부), 기준 혈소판 수 및 $V_{15\,Gy}$(15 Gy 이상 조사된 정상 간 부피)를 통합한 예측 모델을 만들 수 있었다. 이 모델은 ROC 곡선 분석에서 균형 잡힌 적합도, 중간 정도의 차별성 및 0.8629 의 AUC 를 나타내어 간 대상부전 사건 위험을 예측할 수 있는 가능성을 보여주었다.

결론: 우리의 분석은 성별, 간경변의 병인(HBV 여부), 기준 혈소판 수 및 $V_{15\,Gy}$가 간세포암종 환자에 대한 체부정위방사선치료 후 장기적인 간 대상부전 발생에 영향을 미친다는 것을 보여준다. 또한 이 예측모델을 이용해 체부정위방사선치료에 적합한 환자를 선택하고 각 환자에 대한 개별화된 선량 제약을 설정할 수 있다.

핵심 용어: 간세포암종, 체부정위방사선치료, 간 대상부전