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Hepatic toxicity of repeated stereotactic body radiotherapy for recurrent hepatocellular carcinoma using deformable image registration

간세포암종에 대한 반복적인 정위적방사선치료 시 가변영상일치법을 이용한 체적-선량 분포와 간독성의 관계

울산대학교 대학원
의 학 과
이 수 민

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지도교수 윤상민

이 논문을 의학석사 학위 논문으로 제출함

2017년 12월

울산대학교 대학원
의 학 과
이 수 민

이수민의 의학석사 학위 논문을 인준함

심사위원　　조 병 철　　인

심사위원　　김 수 산　　인

심사위원　　윤 상 민　　인

울 산 대 학 교　대 학 원

2017 년　12 월

ABSTRACT

Objective: To evaluate the hepatic toxicity after repeated stereotactic body radiotherapy (SBRT) for recurrent hepatocellular carcinoma (HCC) using deformable image registration (DIR)

Patients and methods: Between January 2007 and December 2015, a total of 85 patients who received two sessions of SBRT for different HCCs were retrospectively analyzed. To calculate the cumulative dose of the first and second SBRT to the normal liver, DIR technique was used for matching the two computed tomography (CT) simulation images. The Dice similarity coefficient (DSC) index was calculated to evaluate the accuracy of DIR. Radiation-induced liver disease (RILD) was defined as the worsening of Child–Pugh score by 2 or more or elevation of transaminases or alkaline phosphatase of at least 5-fold and/or that of bilirubin of at least 3-fold compared to either the upper normal limit or the pretreatment levels without an evidence of disease progression within three months of completing each SBRT. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events, version 4.03.

Results: The median follow-up time was 45 months (interquartile range [IQR], 31–55), and the median interval time between two SBRT sessions was 15 months (IQR, 7–24). Six (7.1%) and twelve (14.1%) patients had Child–Pugh class B cirrhosis before the first and second SBRT, respectively. The median tumor size was 1.7 cm before both SBRT treatments. The median mean liver dose (MLD) was 5.5 Gy (IQR, 3.8–6.9) and 5.0 Gy (IQR, 3.8–6.6), and the median volume of the normal liver was 1210 cm^3 (IQR, 1046–1334) and 1166 cm^3 (IQR, 996–1309) at each SBRT. The mean DSC index value was 0.93 with a standard deviation of 0.03, and DSC index value was >0.9 in 79 (92.9%) registrations. The median cumulative MLD was 9.3 Gy (IQR, 7.6–11.7). Ten (11.8%) patients received cumulative MLD of over 13 Gy, and 13 patients (15.3%) could not achieve the preserved volume of uninvolved liver irradiated less than 15 Gy exceeding 700 cm^3, according to the cumulative dose analysis. RILD was developed only in three patients, and two of them with Child–Pugh class B experienced irreversible deterioration of liver function after the second SBRT. Grade

3 or higher biliary stricture was not observed during the follow-up period.

Conclusion: The DIR method used in the present study provided information on a reliable cumulative dose to the liver. In patients with Child–Pugh class A liver cirrhosis, repeated SBRT for small, recurrent HCC could be safely performed with acceptable hepatic toxicity at a cumulative MLD within or slightly above 13 Gy.

Key words: hepatocellular carcinoma, stereotactic body radiotherapy, re-irradiation, radiation-induced liver disease, deformable image registration

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer, accounting for approximately 6% of all newly diagnosed cancers, and is the second most common cause of cancer-related deaths worldwide.[1] For early stage HCC, established curative treatments include liver transplantation, surgical resection, and percutaneous ablation therapies.[2] Such therapies provide excellent 5-year overall survival up to 70%[3-5]; however, patients with early HCC are not always suitable for these treatments. Liver transplantation is limited to a small number of patients because of its strict indication and lack of donors. Surgical resection could be performed only in patients with sufficient liver function and resectable tumor location.[6, 7] For patients with unresectable small HCC, radiofrequency ablation (RFA) returns high rates of local control with a chance of cure.[8] However, tumors located near the liver surface, such as those at great vessels, gallbladder, and diaphragm, are major obstacles for RFA use.[9] For patients who are not suitable for these curative therapies, transarterial chemoembolization (TACE) is often used based on the results of randomized trials that report improved survival compared with supportive care.[10, 11] However, local control after TACE is not as satisfactory as achieved with curative therapies.[12]

Historically, radiotherapy for HCC was not an attractive option because the liver was known as a radiation-sensitive organ. However, recent improvements in radiotherapy techniques, including image-guided treatment and the knowledge of the partial liver tolerance, have enabled the safe delivery of high radiation doses to focal liver lesion. Many prospective and retrospective studies have reported that stereotactic body radiotherapy (SBRT) achieved excellent local control rate of 85%–100% with acceptable toxicity.[13-20]

One of the major failure patterns after prior treatments, including surgery, RFA, or SBRT, for early stage HCC is another intrahepatic recurrence. Due to this tendency, patients with HCC often require repeated locoregional treatments. If the recurrent lesion was also unsuitable for curative treatments after prior SBRT, the physician would have to consider another SBRT for the new, recurrent HCC. In this case, hepatic toxicity or other late toxicities should be considered before the decision of administering another SBRT. In addition, the information of the cumulative radiation dose to the liver after the first and

second SBRT is necessary in predicting hepatic toxicity. However, few studies have analyzed the safety of and provided dosimetric guidelines for repeated SBRT. Therefore, we evaluated the safety of repeated SBRT for patients with recurrent HCC and investigated the relation between dose–volume parameters and the risk of hepatic toxicities using deformable image registration (DIR).

PATIENTS AND METHODS

Patients

Medical records of patients who received repeated SBRT for recurrent HCC between January 2007 and December 2015 at the Asan Medical Center were retrospectively reviewed. The inclusion criteria for SBRT were described in our previous reports.[17, 21] The decision of repeated SBRT was taken by a radiation oncologist with over 10 years of experience in treating HCC by considering the previous irradiated dose and radiation field. Other local treatments between the SBRT sessions, including surgical resection, TACE, RFA, and/or ethanol injection were allowed. This study was approved by the Institutional Review Board of the Asan Medical Center, and informed consent was waived off because of the retrospective nature of the study.

SBRT procedures

The detailed procedure for SBRT at our institution was described in our previous studies.[17, 21, 22] At least a week before computed tomography (CT) simulation for SBRT, three gold fiducial markers (Standard Gold Soft Tissue Markers; CIVCO Medical Solutions, Kalona, IA) were inserted near the tumor under guidance of ultrasonography.[23] Exceptions were patients who had surgical clips or compact iodized oil that were expected to be identified in pretreatment fluoroscopy for image guidance. Four-dimensional CT simulation with 2.5-mm slice thickness under free breathing was performed in all patients. The gross tumor volume (GTV) was delineated on end-expiratory phase by referring to diagnostic liver dynamic CT or magnetic resonance imaging (MRI). For respiratory-gated radiotherapy, the internal target volume (ITV) was extended from GTV to include tumor movement from 30% to 70% phase. The planning target volume (PTV) margin for setup error was 5 mm. Mainly, 45–60 Gy was administered in three or four fractions covering 85%–90% of PTV. Fiducial or surrogate marker-assisted image guidance using cone-beam CT and fluoroscopy was performed before each fraction of SBRT.

Deformable image registration and cumulative dose calculation

To calculate the cumulative dose to liver, simulation CT images and treatment plan of the first session of SBRT were deformed and registered with the images and plan of the second session. DIR software (Mirada RTx; Mirada Medical Ltd, Oxford, UK), which applies intensity-based voxel to voxel transformation vector, was used for this process. Contours of the liver on each simulation CT images were manually drawn by a radiation oncologist. The Dice similarity coefficient (DSC) index between the deformed liver contour on CT images for the first SBRT and the liver contour obtained on the second SBRT was calculated to evaluate DIR performance (Figure 1).

Cumulative dose–volume parameters to the liver after the first and second SBRT were calculated. Maximal liver doses and mean liver doses (MLDs) were measured. The volume of uninvolved liver (liver volume other than GTV) irradiated more or less than specific cumulative dose (V_{5Gy} to V_{120Gy}, and reverse-V_{5Gy}, or rV_{5Gy} to rV_{120Gy}, increment of 5 Gy, respectively) were also evaluated.

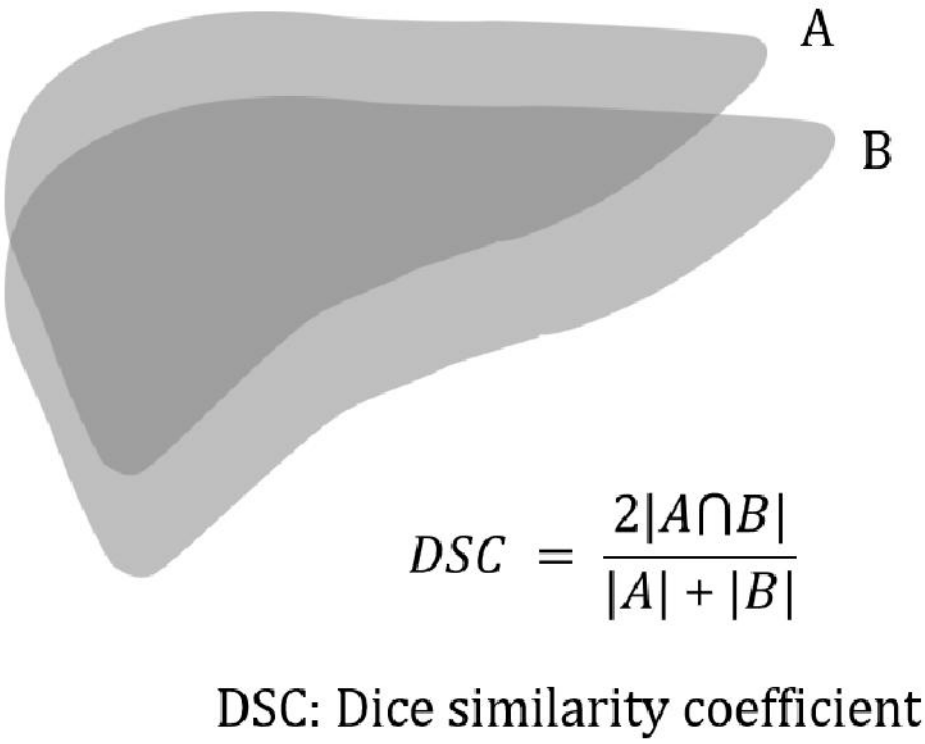

Figure 1. Calculation of the Dice similarity coefficient

Deformed contour of the liver from simulation CT of the first SBRT to the CT of the second SBRT via deformable image registration (A) and manually delineated liver contour of the second (B) were compared.

Evaluation of clinical outcome and hepatic toxicity

All patients were evaluated with physical examination, complete blood count, liver function test, tumor markers, and dynamic enhanced CT or MRI within a month before SBRT. All patients were evaluated during SBRT to assess acute toxicity with laboratory tests and were followed up every 1–3 months after the treatment. Physical examination, complete blood counts, liver function test, tumor markers, and dynamic enhanced CT or MRI were performed at each visit. Response after SBRT was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Best response within six months after SBRT was measured, and response rate was defined as complete (CR) or partial response (PR). Local failure was defined as the recurrence of the treated lesion. Radiation-induced liver disease (RILD) was defined when one of the following conditions was satisfied without disease progression within three months after SBRT: (1) an increase of 2 or more of Child–Pugh score or (2) an elevation in aspartate aminotransferase (AST)/alanine aminotransferase (ALT)/alkaline phosphatase (ALP) of at least 5-fold and/or that of bilirubin of at least 3-fold compared to either the upper normal limit or the pretreatment level corresponding to Grade 3 or higher hepatic toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Late toxicities including biliary toxicity, chronologic change of liver function, and image finding were also evaluated.

Statistical analysis

The follow-up duration and survival time were measured from the start date of the first SBRT. The Kaplan–Meier method and log rank test were used for survival analysis. Chi-square, t-test, and logistic regression analysis were used to compare risks of parameters. A p value of <0.05 was considered statistically significant. SPSS version 21 (IBM SPSS Statistics, Armonk, NY) was used for all statistical analyses.

RESULTS

Characteristics of patients and SBRT

A total of 85 patients with 170 SBRT sessions were analyzed. The characteristics of patients at each SBRT session are summarized in Table 1. Median age at the first SBRT was 64 (interquartile range [IQR], 56–70) years old. HBV infection (70.6%) was most common viral etiology. Median tumor size was 1.7 cm in both (IQR, 1.5–2.2 and 1.4–2.2 for the first and second SBRT, respectively), and tumors larger than 3 cm at the longest diameter in each session of SBRT were only in 8.2% and 5.9% in the first and second SBRT, respectively. Only four patients received SBRT as the first-line treatment, and 13 (15.3%) patients underwent surgery before the first SBRT. The median interval between the two SBRT sessions was 15 months (IQR, 7–24). During this interval, 38 (44.7%) patients received other locoregional treatments with a median number of 2 (IQR, 1–3). The most commonly used dose-fractionation scheme was 45 Gy in three fractions. There was no significant difference in tumor size and volume of GTV and PTV between two SBRT sessions. The MLD was 5.5 Gy and 5.0 Gy for the first and second SBRT, respectively.

Table 1. Characteristics of patients and each session of SBRT

n = 85	First SBRT	Second SBRT
Age (years)		
Median (IQR)	64 (56–70)	65 (57–71)
Sex		
Male	67 (78.8%)	
Female	18 (21.2%)	
Etiology		
Hepatitis B virus	60 (70.6%)	
Hepatitis C virus	18 (21.2%)	
Non-B, Non-C	7 (8.2%)	
ECOG PS		
0 – 1	82 (96.5%)	83 (97.6%)
2	3 (3.5%)	2 (2.4%)
Previous local treatment*		
No	4 (4.7%)	47 (55.3%)
Yes	81 (95.3%)	38 (44.7%)
Surgery	13 (15.3%)	0 (0.0%)
Sessions of treatment		
Median (IQR)	3 (2–6)	2 (1–3)
Pre-SBRT Child–Pugh score		
5–6	79 (92.9%)	73 (85.9%)
7	2 (2.4%)	8 (9.4%)
8–9	4 (4.7%)	4 (4.7%)
Interval (months)		
Median (IQR)	15 (7–24)	
Tumor size (cm)		
Median (IQR)	1.7 (1.5–2.2)	1.7 (1.4–2.2)
Volume of GTV (cm^3)		
Median (IQR)	3.6 (2.0–5.9)	2.9 (1.7–4.6)
Volume of PTV (cm^3)		
Median (IQR)	21.0 (15.6–33.2)	20.9 (15.1–27.5)
Volume of normal liver (cm^3)		

Median (IQR)	1210 (1046–1334)	1166 (996–1309)
Mean liver dose (Gy)		
Median (IQR)	5.5 (3.8–6.9)	5.0 (3.8–6.6)
Dose fractionation		
36 Gy/3fx	7 (8.2%)	3 (3.5%)
45 Gy/3fx	60 (70.6%)	63 (74.1%)
48 Gy/4fx	2 (2.4%)	2 (2.4%)
60 Gy/4fx	15 (17.6%)	12 (14.1%)
60 Gy/3fx	1 (1.2%)	2 (2.4%)
Others	0 (0.0%)	3 (3.5%)[†]

[*]Local treatments include transarterial chemoembolization, radiofrequency ablation, percutaneous injection of ethanol, and surgical resection. Previous local treatment in the second SBRT session is the value of the interim period between the first and second SBRT.

[†]Other dose fractionations include 40 Gy/4fx, 30 Gy/3fx, and 32 Gy/4fx for patients with Child–Pugh class B cirrhosis.

SBRT, stereotactic body radiotherapy; IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group performance status; GTV, gross target volume; PTV, planning target volume

Deformable image registration and cumulative liver dose

DIR was performed in all patients, and an example of DIR is presented in Figure 2. The mean DSC index value was 0.93 with a standard deviation of 0.03. The DSC index value was >0.9 in 79 (92.9%) registrations, with a value <0.85 only in one registration. The DSC index of rigid registration (single transformation vector for all voxels) was always inferior to that of DIR. DSC indices of DIR and rigid registration are presented in Figure 3.

The median cumulative MLD was 9.3 Gy (range, 4.3 – 19.5 and IQR, 7.6 – 11.7). Ten (11.8%) patients received cumulative MLD of over 13 Gy, including an RILD patient who received 19.3 Gy. In addition, 13 patients (15.3%) could not achieve the preserved volume of uninvolved liver irradiated less than 15 Gy exceeding 700 cm^3 ($rV_{15Gy} > 700\ cm^3$). The detailed cumulative dose–volume relationship of the liver is shown in Table 2, and the histogram of cumulative dose in mean value with standard deviation is shown in Figure 4.

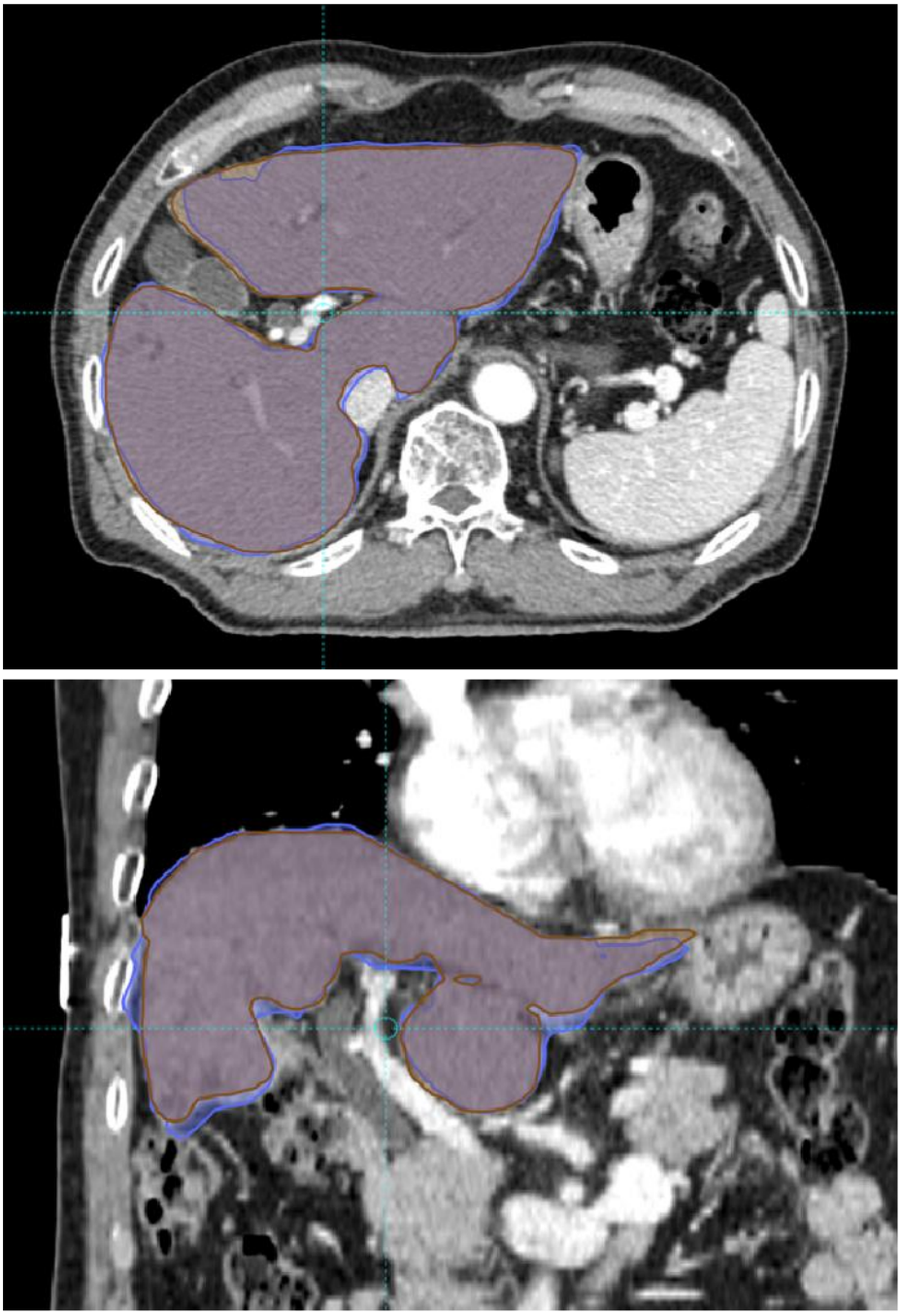

Figure 2. An example of deformable image registration

Contours of liver on each simulation CT image were manually drawn. The contour of liver on the first simulation CT was deformed and was registered onto the second CT image. The Dice similarity coefficient (DSC) was calculated between manually drawn contours of liver in second simulation CT (brown) and deformed contour from first simulation CT (blue). The DSC value of this patient was 0.94.

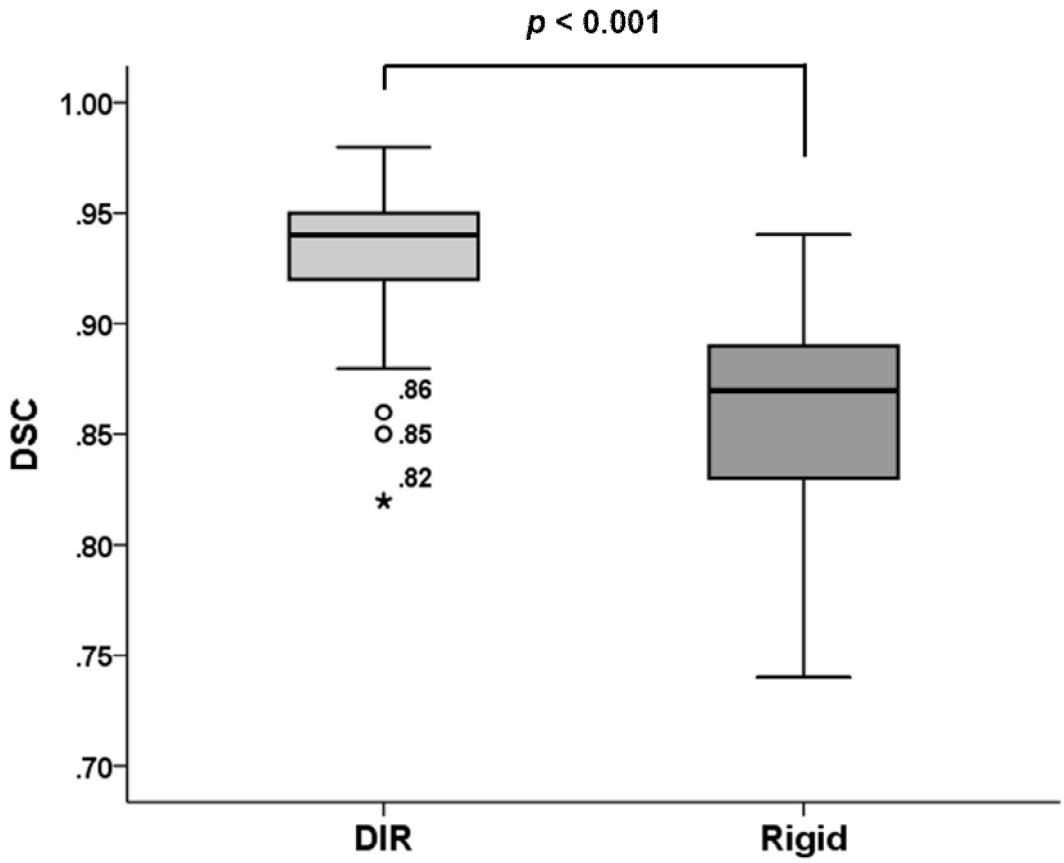

Figure 3. A box plot of the Dice similarity coefficient indices of deformable and rigid image registrations

Table 2. Summary of cumulative dose–volume parameters

	V_{5Gy}	V_{10Gy}	V_{15Gy}	V_{20Gy}	V_{25Gy}	V_{30Gy}	V_{40Gy}	V_{50Gy}
Volume (cm^3)								
Median	553	339	216	151	108	82	49	22
IQR	456–682	272–447	157–316	107–219	73–156	54–110	32–64	9–35
Volume (%)								
Median	49.8	28.8	19.6	13.8	9.5	7.2	4.1	1.8
IQR	39.1–61.5	22.6–39.2	14.1–27.8	9.7–19.1	6.8–13.8	4.7–10.2	2.5–5.7	0.6–3.1
	V_{60Gy}	V_{75Gy}	V_{90Gy}	V_{105Gy}	V_{120Gy}	D_{max}	rV_{15Gy} (cm^3)	MLD (Gy)
Volume (cm^3)								
Median	4	0	0	0	0	66.4	871	9.3
IQR	0–15	0–1	0–0	0–0	0–0	56.9–79.5	743–1051	7.6–11.6
Volume (%)								
Median	0.3	0	0	0	0		**<700 cm^3**	**>13 Gy**
IQR	0–1.3	0–0.1	0–0	0–0	0–0		*n* = 13 (15.3%)	*n* = 10 (11.8%)

Volume of the uninvolved liver (cm^3 or %) irradiated at X Gy (V_{XGy})

IQR, interquartile range; rV_{15Gy}, reverse V15Gy (the volume of uninvolved liver irradiated below 15 Gy); D_{max}, maximal dose; MLD, mean liver dose

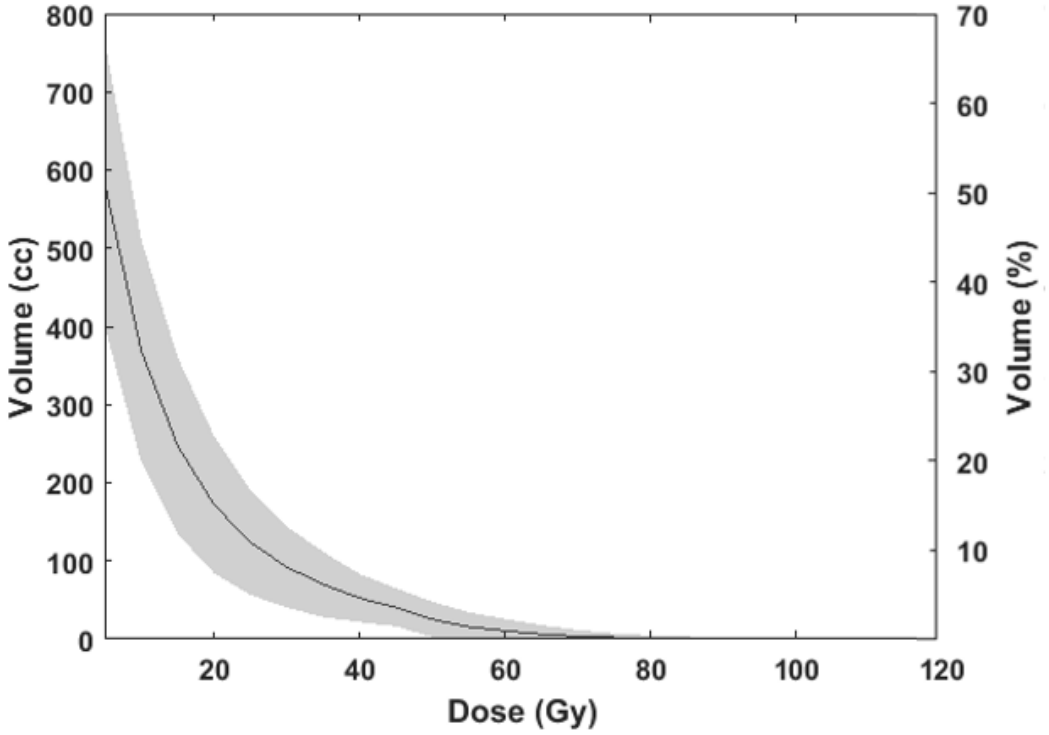

Figure 4. Cumulative dose–volume histogram of uninvolved liver after two sessions of SBRT (mean ± standard deviation)

Clinical outcomes

Overall response rate was 74.7% (CR in 93 and PR in 34 lesions) within six months after each SBRT. Tumor response rate was comparable for the two sessions of SBRT (76.5% vs. 72.9%, p = 0.708). After the median follow-up time of 45 months (IQR, 31–55), the overall 3-year local control rate was 93.3% in all treatment sessions. The 3-year local control rates of the first and second SBRT were not significantly different (94.9% vs. 90.4%, p = 0.667).

Hepatic toxicity and liver function

After 170 sessions of SBRT, only three cases of RILD developed. One patient with Child–Pugh class A and sufficient liver volume (1,274 cm^3) experienced Grade 3 AST/ALT elevation after the first SBRT of 60 Gy administered in three fractions. It spontaneously resolved within two months with supportive care only. He did not experience liver function deterioration or RILD after the second SBRT of 45 Gy administered in three fractions. The other two patients who experienced RILD after their second SBRT of 45 Gy administered in three fractions had Child–Pugh class B (Child–Pugh score 7) cirrhosis before the second SBRT. A 70-year-old man did not suffer RILD or any hepatotoxicity after the first SBRT. However, liver function deteriorated rapidly with development of ascites and hepatic encephalopathy after the second SBRT, and he died within two months. His cumulative MLD was 12.5 Gy, and volume of normal liver was 1139.3 cm^3. The last patient also experienced an increase of Child–Pugh score by 2 after the second SBRT. His cumulative MLD was 19.3 Gy and his normal liver volume was 794 cm^3. He is alive at the time of writing this report but showed gradual worsening of liver function during the follow-up period. Summary of these patients who experienced RILD are shown in Table 3, and the change of Child–Pugh class of all patients along the course of SBRT are shown in Figure 5.

Table 3. Summary of the cases who developed of RILD after the first and second SBRT

Case	Time of occurrence	Pre-SBRT C–P class (score)	Dose fractionation	Volume of normal liver (cm^3)	Cumulative MLD (Gy)	Hepatotoxicity	Post-SBRT C–P class (score)
67/M	First	A (5)	60 Gy/3fx	1274 cm^3	5.7 Gy	Gr 3 (AST/ALT)*	A (5)
70/M	Second	B (7)	45 Gy/3fx	1139 cm^3	12.5 Gy	Gr 3 (Bilirubin)	C (12)*
58/M	Second	B (7)	45 Gy/3fx	794 cm^3	19.3 Gy	Gr 2 (Bilirubin)*	B (9)*

*Toxicities that meet the pre-defined criteria of radiation induced liver disease

SBRT, stereotactic body radiotherapy; C–P, Child–Pugh; MLD, mean liver dose; Gr, grade; AST, aspartate aminotransferase; ALT, alanine aminotransferase

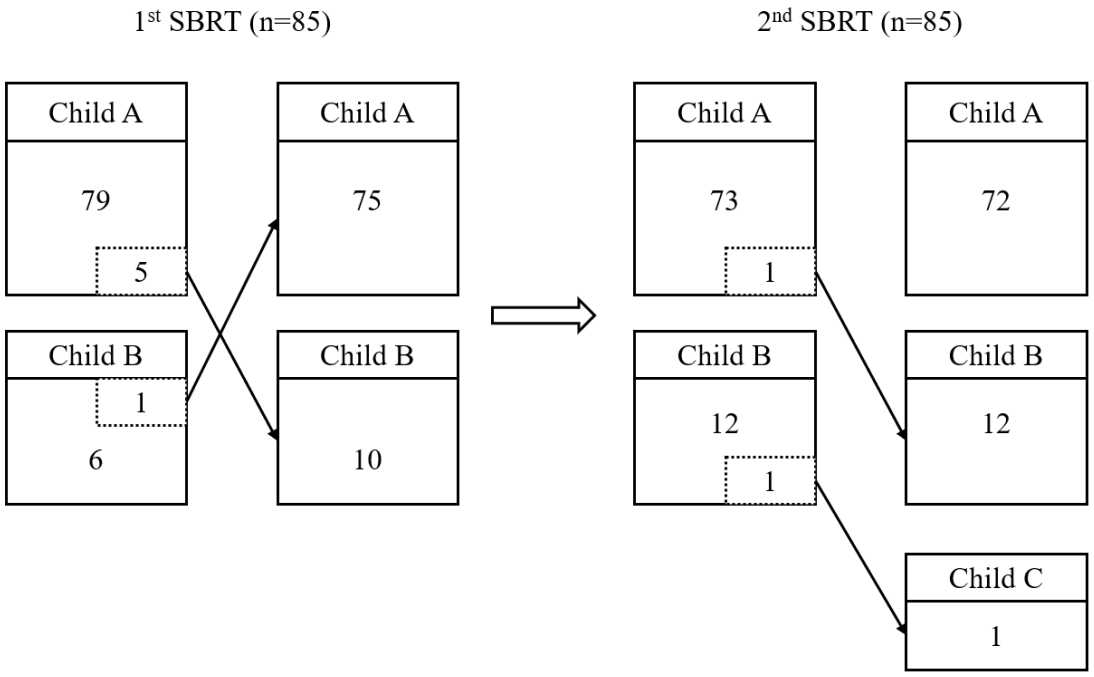

Figure 5. Changes of the Child–Pugh classification in repeated SBRT

Late hepatic effect after repeated SBRT

There was no Grade 3 or higher biliary stricture caused by SBRT during the follow-up periods. There were six cases (7.1%) of mild bile duct dilatation in the correlated area with previous SBRT, but these did not lead to elevation of bilirubin levels or the need of endoscopic intervention. In serial follow-up CT images, focal parenchymal change and hepatic atrophy with or without capsular retraction was shown in almost all the patients; however, no other specific finding was observed in overlapped high–dose region exceeding 60 Gy.

DISCUSSION

Only few studies have evaluated the safety of repeated SBRT thus far. Some obstacles, such as application of various treatments due to frequent intrahepatic recurrence, the natural deterioration of liver function due to liver cirrhosis, and inaccuracies of the calculation of cumulative dose after SBRT, have made it difficult to evaluate the safety of repeated SBRT. Although the applicability of the DIR tool to the upper abdominal organs has not been well evaluated because of such inaccuracies,[24] the relatively high DSC values presented in this study may help achieve a reliable cumulative dose calculation by DIR. Low DSC values in some cases are generally due to low contrast between the liver and newly developed ascites or large vessels in the liver contours; therefore, further research is warranted to improve the registration accuracy.

In the present study, we found that repeated SBRT could be performed safely while maintaining high rates of local tumor control. When performing SBRT for primary liver cancers, Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommends a normal liver volume of more than 700 cm^3 to be irradiated below 15 Gy for 3–5 fractions, with the MLD not exceeding 13 Gy for three fractions.[25] Even if the limitation of this single session was applied to our case series directly, the violation of the dose recommendation was only 15.3% or less. SBRT was performed on relatively small HCC with a median tumor size of 1.7 cm, and there was not much deterioration of liver function during the interim period. Repeated SBRT in such carefully selected patients could be safely performed with an overall incidence of RILD being only 3.5%. However, the patients who had the baseline liver function of Child–Pugh class B and had a relatively small volume of the normal liver (<800 cm^3) experienced unrecoverable liver function deterioration after the second SBRT. Care should be taken before recommending repeated SBRT in such clinical conditions.

RILD has been defined differently in many studies, but as a non-classic RILD, elevation of liver enzyme or elevation of a Child–Pugh score by 2 or more is a widely used index. In the present study, one patient experienced RILD with elevation of liver enzyme after the first SBRT but recovered with supportive care. However, after the second SBRT, the Child–Pugh

score elevated by ≥ 2 in two patients and was not restored, and the elevation of liver enzyme was not observed in these patients. The underlying pathology of non-classic RILD is not clearly understood, but the deterioration of liver function with the elevation of Child–Pugh scores may be a more significant clinical endpoint than with the elevation of liver enzyme.

So far, few studies have analyzed the results of repeated radiotherapy for recurrent HCC with a various fractionation scheme. Lo et al.[26] analyzed the results of repeated SBRT using CyberKnife with median 41 Gy (range, 34–60) in the first and 40 Gy (range, 25–50) in the second SBRT in 14 HCC patients. They defined non-classic RILD as Grade 3 or higher toxicity according to CTCAE version 3.0 and reported that RILD occurred in one (7%) after the second SBRT, which was resolved with symptomatic management. Seol et al.[27] also reported that tolerable re-irradiation without RILD could be performed in 43 HCC patients. However, these two studies did not show the cumulative radiation dose of repeated radiotherapy using the image registration technique.

Kimura et al.[28] performed repeated SBRT in 24 patients for intrahepatic recurrences with 40 or 48 Gy in four fractions and reported seven (29%) cases of Grade 3 or higher toxicities which included AST/ALT elevation, decreased platelet count, and ascites. These toxicities occurred significantly more in Child–Pugh class B patients. We assume that compared with our study, their study had increased frequency of incidence of toxicity because of a higher proportion of Child–Pugh class B (17% at initial and 25% at second or beyond) patients and a marginally higher cumulative MLD of 13.1 Gy. Oshiro et al.[29] showed the results of repeated proton beam therapy using DIR and reported no classic or non-classic RILD among 83 patients who received repeated proton therapy with a maximal delivered dose to the liver ranging from 66.7 to 248.1 GyE. However, as with a single session of SBRT,[21] repeated SBRT in patients with advanced liver cirrhosis seems to have a higher hepatic toxicity.[30, 31] Further research is needed to confirm the safety of repeated SBRT in patients with chronic liver disease.

The current study also showed low risk of late biliary toxicity as well as RILD. Several studies have suggested that high-dose radiotherapy for central lesions may be a risk factor for biliary complications.[32, 33] However, there was no Grade 3 or higher biliary stricture, and only six patients had Grade 1 of mild dilation of bile duct without significant bilirubin

elevation or the need for endoscopic intervention. In addition, the irradiated liver showed focal atrophy in almost all the patients, which was a previously well-known image finding.[34] When repeated SBRT was performed, additional atrophy was observed, but additional findings, such as distortion of vascular structure or biliary stricture, were not observed in the overlapping high-dose area. These findings suggest that after the focal atrophy due to loss of damaged hepatocytes has progressed, the previous high-dose radiation is relatively less influential in terms of the safety of repeated SBRT.

The present study had certain limitations. Because this was a retrospective study, the results may have a potential bias and should be interpreted cautiously. It was also difficult to define the reason for hepatic function deterioration after SBRT in patients with a background of liver cirrhosis. In fact, other confounding factors, such as other locoregional treatments, worsening of the cirrhosis itself, or other hepatotoxic effects, could also be related with these hepatic toxicities. Finally, it was difficult to recommend the maximum tolerable dose level as a guideline for repeated SBRT because the incidence of RILD was relatively low. However, to our knowledge, the current study is the largest series evaluating hepatic toxicity after repeated SBRT for HCC and was performed according to a relatively consistent protocol. In addition, the cumulative dose was reliably calculated using the DIR software, which would aid in clinical judgment.

CONCLUSION

The DIR method, used in the present study, provided reliable information on cumulative dose to the liver. In patients with Child–Pugh class A cirrhosis, repeated SBRT for small, recurrent HCC could be safely performed with acceptable hepatic toxicity at a cumulative MLD within or marginally above 13 Gy. The safety of repeated SBRT in patients with Child–Pugh class B needs further evaluation.

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국 문 요 약

목적: 재발한 간세포암종에 대한 반복적인 체부 정위방사선치료 시 가변영상일치법을 이용하여 누적 체적-선량 분포를 계산하고 간독성을 평가하고자 하였다.

대상 및 방법: 2007 년 1 월부터 2015 년 12 월까지 서로 다른 간세포암종에 대하여 2 회의 체부 정위방사선치료를 시행 받은 총 85 명의 환자를 후향적으로 분석하였다. 정상 간에 조사된 누적 선량을 계산하기 위해, 두 전산화 단층촬영 모의치료영상을 가변영상일치법을 이용하여 맞추었다. 가변영상일치법의 정확도를 평가하기 위해 dice similarity coefficient (DSC)를 계산하였다. 방사선간질환은 방사선치료 완료 후 3 개월 이내에 질병의 악화 증거가 없으면서 혈청 간 효소 수치 또는 혈청 빌리루빈 수치가 정상 상한치 또는 치료 전 수치의 각각 5 배, 3 배 이상으로 증가하거나, Child-Pugh 점수가 2 점 이상 상승한 경우로 정의하였다. 독성은 Common Terminology Criteria for Adverse Events version 4.03 에 따라 분석하였다.

결과: 중간 추적관찰기간은 45 개월 (사분범위 31 – 55)이었고, 두 체부 정위방사선치료간의 중간 간격은 15 개월 (사분범위 7 – 24)이었다. Child-Pugh class B 인 환자는 첫번째 체부 정위방사선치료 시에 6 명 (7.1%), 두번째 12 명 (14.1%)였다. 중간 종양 크기는 두 번의 체부 정위방사선치료 모두에서 1.7 cm 였다. 정상 간에 조사된 평균 선량은 첫번째 체부 정위방사선치료 시 5.5 Gy (사분범위 3.9 – 6.9), 두번째 5.0 Gy (사분범위, 3.8 – 6.6)였고, 정상 간 용적은 첫번째 1210 cm^3 (사분범위, 1046 – 1334), 두번째 1166 cm^3 (996 – 1309)였다. 평균 DSC 값은 0.93 이었고 표준편차는 0.03 이었는데, 79 (92.9%)개의 영상정합에서 0.9 이상의 DSC 값을 보였다. 정상 간에 조사된 누적 평균 선량은 9.3 Gy (사분범위, 7.6 – 11.7)였다. 이 중 10 명(11.8%)의 환자가 정상 간에 조사된 누적 평균 선량이 13 Gy 를 초과하였고, 13 명(15.3%)의 환자가 15 Gy 이하로 조사되는 정상 간의 용적이 700 cm^3 이하였다. 방사선간질환은 3 명의 환자에서만 발생하였는데, 이 중 Child-Pugh class B 였던 2 명은 간기능의 악화가 다시 회복되지 않았다. 에 따른 3 도 이상의 담도 독성은 추적관찰기간동안 관찰되지 않았다.

결론: 가변영상일치법은 간에 조사된 누적 선량에 대한 신뢰할 만한 정보를 제공하였다. Child-Pugh class A 의 간기능을 가진 환자에서 크기가 작은 간세포암종에 대해 반복적인 체부 정위방사선치료를 시행할 경우, 정산 간에 조사되는 누적 평균 선량이 13 Gy 이내이거나 약간 높은 정도일 때 안전하게 시행할 수 있다.

핵심용어: 간세포암종, 체부 정위방사선치료, 재방사선치료, 방사선간질환, 가변영상 일치법