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Predictors of Adverse Gastrointestinal Events After Stereotactic Body Radiation Therapy for Liver Tumors

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Abstract. *Background/Aim: To identify predictors of adverse gastrointestinal (GI) events related to stereotactic body radiation therapy (SBRT) for liver tumors. Patients and Methods: We retrospectively analyzed 56 patients who underwent SBRT for liver tumors at our institution between 2016 and 2021. The α/β ratio of the GI tract (stomach, duodenum, and large intestine) was assumed to be 3 Gy in the Linear-Quadratic model (LQ model). The dose to the GI tract, that is, the biologically effective dose 3 (BED3) was converted to a 2 Gy equivalent dose (Gy2/3=2 Gy equivalent dose, α/β=3). Using this 2 Gy equivalent dose, predictors of adverse GI events of Grade 2 or higher were investigated. Results: The median observation period was 10 months (0-40 months) and median age was 77 years (range=29-93 years). Forty-three of the 56 patients had hepatocellular carcinoma and the other 13 had metastatic liver tumors. Tumors were irradiated with 30-54 Gy/5-18 fractions of planning target volume D95% prescription (80% isodose). Eight of the 56 patients had Grade 2 or higher adverse GI events. By univariate analysis, GI D1cc, Dmax, V20, V25, V30, and V35 were all significant predictors of Grade 2 or higher adverse GI events. Among these, gastrointestinal V35 was the most significant predictor of Grade 2 or higher adverse GI events. Conclusion: For SBRT of liver tumors, GI V35 was the best predictor of Grade 2 or higher adverse GI events.*

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Stereotactic body radiation therapy (SBRT) is a high-precision radiation technique that delivers a single large dose to a tumor target, while sparing surrounding normal tissue. Prospective and retrospective studies of SBRT for liver tumors have demonstrated excellent local control (>80-90%) with minimal toxicity (1-6). However, for hepatocellular carcinoma with cirrhosis of Child-Pugh score 8 or more, prognosis after liver SBRT was suboptimal (7). In Addition, the gastrointestinal (GI) tract is highly radiosensitive and high doses of radiation may cause damage, such as ulceration, bleeding, and perforation. Therefore, SBRT for locations in close proximity to the gastrointestinal tract should be performed with caution. Sanuki *et al*. and Tsurugai *et al*. reported that the occurrence of GI events was acceptable if GI maximum dose to planning organ at risk volume (Dmax) and dose covering 1.0cc of planning organ at risk volume (D1cc) were followed (8, 9). However, few studies have analyzed other predictors. The purpose of this study was to identify further useful predictors of adverse GI events after SBRT for liver tumors.

Patients and Methods

Patients. We retrospectively analyzed 56 patients who underwent first-time SBRT for liver tumors at our institution between January 2016 and November 2021. SBRT was performed in patients with Child-Pugh classification A or B, ineligible for surgery, percutaneous radiofrequency ablation (RFA) or transarterial chemoembolization (TACE), or who had failed repeated RFA or TACE. This retrospective review was approved by our institutional review board, and the requirement for written informed consent was waived for retrospective data collection.

Radiotherapy. Infrared reflective markers were placed on the patient's abdomen to account for respiratory movement of the tumor. Respiratory waveforms were obtained by capturing the movement of the abdominal wall due to respiration with a dedicated camera, and 10 or 20 phase computed tomography (CT) images were obtained for each respiratory phase (RPM Respiratory Gating System Version 1.7, Varian Medical Systems Inc., Palo Alto, CA, USA). Non-contrast planning CT was performed and a gross tumor volume (GTV) was set in each of the inspiratory and expiratory phases

Table I. *Patient characteristics*.

Factor	Median/Group	Range, n
Age	77	29-93
Sex	Male/female	37/19
Diagnosis	HCC/Metastasis	43/13
T factor for HCC	T1/2/3/4	24/14/1/4
Child-Pugh classification	A/B	46/10
Pre-irradiation performance status	≥2/<2	9/47
Background liver (Etiology)	Hepatitis B/Hepatitis C/FALD/	5/19/3/
	Alcoholicity/NASH/Normal liver	6/9/14
Tumor size (cm)	3.0	0.9-9.0
Anticoagulant	Yes/No	15/41
Previous treatment at the same site	Yes/No	21/35
Prescription Specification	PTV D95% (80% isodose)	51
	PTV D90% (100% isodose)	4
	PTV D50% (80% isodose)	1
Irradiation technique	VMAT/3D-CRT	48/8

HCC: Hepatocellular carcinoma; FALD: Fontan-associated liver disease; NASH: nonalcoholic steato-hepatitis; PTV: planning target volume; VMAT: volumetric modulated arc therapy; 3D-CRT: Three-dimensional conformal radiation therapy.

(GTV-in, GTV-ex) by fusing contrast-enhanced magnetic resonance imaging (MRI) and contrast-enhanced CT. A clinical target volume (CTV) was created with a 3 mm margin around the GTV-in, GTV-ex (CTV-in, CTV-ex). The internal target volume (ITV) was established by merging CTV-in and CTV-ex, and the planning target volume (PTV) was created with a 5 mm margin surrounding the ITV. The planning organ at risk volume (PRV) was defined as the gastrointestinal tract (stomach, duodenum, intestine) plus an additional 3 mm margin. Doses ranged from 2.5-8 Gy (median 7 Gy)/fraction, with a total dose of 30-54 Gy (median 40 Gy). Forty Gy/5 fractions was the basic dose, with the total dose reduced in patients with poor liver function and the number of fractionated doses reduced in patients with close proximity to the gastrointestinal tract. Dose constraints for the gastrointestinal tract were set at Dmax (The maximum dose to the digestive tract (stomach, duodenum, intestine)) <25 Gy/5 fractions, 30 Gy/8 fractions, and D1cc (the dose covering 1.0 cc of PRV) <20 Gy/5 fractions, 24 Gy/8 fractions.

As a rule, volumetric modulated arc therapy (VMAT) was used, and irradiation was performed using the PTV D95% prescription (80% isodose). Treatment plans were created using Eclipse ver.13.7 (Varian Medical Systems Inc.). The irradiation device was True beam (Varian Medical Systems Inc.). In the case of patients with tumors in close proximity to the gastrointestinal tract, treatment was performed under fasting conditions (fasting for 3 h, no water consumption for 1 h). Image-guided radiation therapy (IGRT) was performed for each irradiation.

Follow-up. After radiotherapy, patients were followed up with periodic visits and imaging studies [Gadolinium-ethoxybenzyl MRI (Gd/EOB MRI) or dynamic contrast-enhanced CT, or abdominal echocardiography if contrast was not available]. Imaging evaluations, such as CT, MRI, and abdominal echo were usually performed around 3 months after SBRT for evaluation purposes, and in principle every 3 months thereafter. Upper gastrointestinal endoscopy was performed before SBRT in 25 patients (44.6%) and after SBRT in 21 patients (37.5%). Most were performed before or after irradiation as a follow-up for esophageal varices. If a patient complained of any gastrointestinal symptoms after SBRT, it was performed for closer examination. Local response to treatment was determined by the modified RECIST (10). When contrast-enhancement was not available, non-contrast CT/MRI or abdominal ultrasonography was used to evaluate the patients with the new response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). New lesions within the PTV were defined as local recurrence, and new lesions outside the PTV were defined as intrahepatic recurrence.

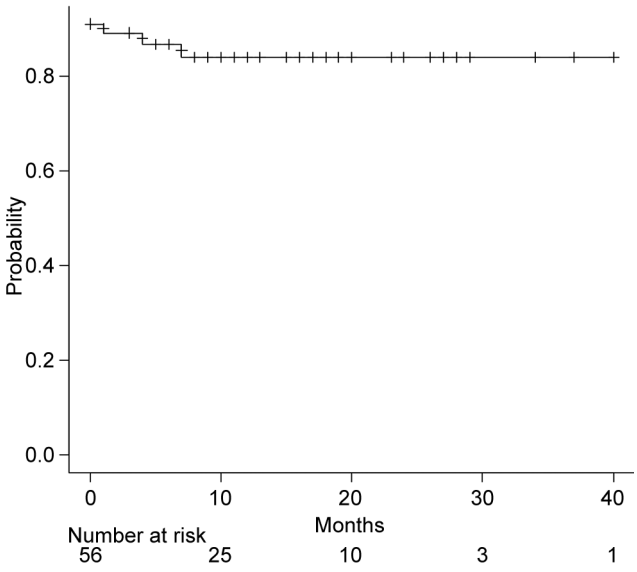

Figure 1. *Kaplan-Meier curve for event-free survival of Grade 2 or higher gastrointestinal events*.

Statistical analysis. Overall survival (OS) and local control (LC) were estimated using the Kaplan-Meier method. The initial date of

Table II. *Univariate analysis*.

Factor	*p*-Value
Age	0.06
Sex (male *vs*. female)	0.7
Diagnosis (primary or metastasis)	0.37
Child-Pugh classification (A *vs*. B)	1
PS before irradiation	0.6
Previous treatment to the same site (yes *vs*. no)	1
D1cc	<0.01
Dmax	<0.01
V20	<0.01
V25	<0.01
V30	<0.01
V35	<0.01
Molecular targeted drugs (yes *vs*. no)	0.32
Anticoagulant (yes *vs*. no)	0.19
Supportive care (yes *vs*. no)	0.7

All doses were converted to 2 Gy equivalent dose with α/β ratio of 3 Gy. Supportive care was determined by the use of proton pump inhibitors and gastric mucosal protection during irradiation. PRV: Planning organ at risk volume; D1cc(Gy): dose covering 1.0cc of PRV; Dmax(Gy): maximum dose to PRV; Vx(ml): PRV volume receiving above a certain dose.

Table III. *Receiver operating characteristic (ROC) curve analysis for each dose parameter.*

Parameters	AUC	Cut-off (Gy2/3, ml)	Incidence of adverse GI events of Grade 2 or higher
D1cc	0,911	<37.38	0/38 (0%)
		≥37.38	8/18 (44.4%)
Dmax	0,862	<38.39	0/33 (0%)
		≥38.39	8/23 (34.8%)
V20	0,893	<1.7	0/37 (0%)
		≥1.7	8/19 (42.1%)
V25	0,904	<1.3	0/37 (0%)
		≥1.3	8/19 (42.1%)
V30	0,918	<0.9	0/36 (0%)
		≥0.9	8/20 (40.0%)
V35	0,924	<0.5	0/35 (0%)
		≥0.5	8/21 (38.1%)

All doses were converted to 2 Gy equivalent dose with α/β ratio of 3 Gy. PRV: Panning organ at Risk Volume; D1cc(Gy): dose covering 1.0cc of PRV; Dmax(Gy): maximum dose to PRV; Vx(ml): PRV volume receiving above a certain dose; AUC: area under the ROC curve.

OS was the first day of SBRT and the termination date was the date of death; the initial date of LC was the first day of SBRT and the termination date was the date of the imaging test on which recurrence was diagnosed. Adverse GI events were evaluated according to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE v5.0). The possible relationship between toxicity and treatment was determined retrospectively using all available data. Event-free survival (EFS) for Grade 2 or higher GI events was investigated using the Kaplan-Meier method. Gastrointestinal doses were assessed using dose-volume histograms (DVH). Dmax (Gy), D1cc (Gy), and the PRV volume receiving above a certain dose [V20, 25, 30, 35 (ml)] were recorded. We divided the groups into two groups, those in which Grade 2 or higher gastrointestinal adverse events occurred and those in which they did not. Each factor was evaluated in a univariate analysis using *t*-tests and chi-square tests, and factors with significant differences between the two groups were analyzed. Receiver operator characteristic curve (ROC) analysis and area under the curve (AUC) were performed for each DVH parameter with significant differences between the two groups, and the most significant predictors were considered, assuming that the larger the AUC, the more useful the predictor. *p*-Values <0.05 were considered statistically significant. Analysis was performed using EZR (EasyR ver.1.55 Jichi Medical University Saitama Medical Center, Saitama, Japan) (11), a graphical user interface (GUI) of R (The R Foundation for Statistics Computing ver.4.1.2).

Results

Patients. The median observation period was 10 months (0-40 months). Patient characteristics are summarized in Table I.

Oncological outcomes. For 43 patients with primary liver cancer (hepatocellular carcinoma and intrahepatic cholangiocarcinoma), 1-year OS was 90.9%, 2-year OS was 75.8%, 1-year LC was 78.6%, and 2-year LC was 58.2%. For irradiation of metastatic liver tumors, 1-year OS was 100.0% and 1-year LC was 83.3%. The effective rate was complete response (CR) in 16 patients (28.6%), partial response (PR) in 16 patients (28.6%), stable disease (SD) in 18 patients (32.1%), progressive disease (PD) in 2 patients (3.6%), and failure to evaluate in 4 (7.1%) with a response rate of 57.2%.

Toxicities. Of the 56 patients, 8 (14.3%) had Grade 2 or higher adverse GI events. One had Grade 3 duodenal bleeding, 1 had Grade 3 colonic bleeding, 1 had Grade 2 duodenal bleeding, 4 had Grade 2 gastroduodenitis, and 1 had Grade 2 colitis. Five of the 8 patients underwent endoscopy before treatment, but none were found to have ulcers. Two patients with gastrointestinal bleeding Grade 3 were both taking anticoagulants (one took Warfarin and one took Edoxaban).

Three-month event-free survival (EFS) for Grade 2 or higher GI events was 89.2%, 6-month EFS was 86.8%, and 1-year EFS was 84.1% (Figure 1).

In univariate analysis, gastrointestinal D1cc, Dmax, V20, V25, V30, and V35 were all significant predictors of Grade 2 or higher adverse GI events (Table II).

ROC curve analysis of each dose parameter showed that gastrointestinal V35 was the most significant predictor of Grade 2 or higher adverse GI events due to the largest AUC.

Table IV. *Study on the association between gastrointestinal adverse events and dose-volume effects after stereotactic body radiation therapy (SBRT).*

Author(s) (Year)	Site	Number of lesions	Prescribed dose	Dose constraints and adverse GI events
Huang *et al*. (2012) (12)	Pancreatic cancer	46	30-42 Gy/15 fractions	Duodenal V25 >45%, V35 >20% most predictive of Grade 3 or higher adverse GI events
Yoon *et al*. (2013) (13)	HCC	90	3.5 (2-5) Gy/fraction Total 37.5 (30-50) Gy	Stomach V25Gy ≥6.3%, duodenal V35Gy ≥5.4% most predictive of Grade 2 or higher adverse GI events
Sanuki *et al*. (2014) (8)	HCC	185	35-40 Gy/5 fractions	Stomach, duodenum, and large intestine D1cc <25 Gy/5 fractions; no adverse GI events above Grade 3
Tsurugai *et al*. (2021) (9)	HCC	73	42 Gy/14 fractions	Gastrointestinal Dmax <48 Gy/14 fractions and only one Grade 3 and two Grade 2 adverse GI events.
Current study	HCC Metastatic liver tumors	56	30-54 Gy/5-18 fractions	Gastrointestinal V35 Gy ≥0.5 ml most predictive of Grade 2 or higher adverse GI events

HCC: Hepatocellular carcinoma.

The cut-off value was 0.5 ml, and the incidence of Grade 2 or higher adverse GI events was 38.1% (8 of 21 patients) for V35 ≥0.5 ml and 0% (0 of 35 patients) for V35 <0.5 ml (Table III).

Discussion

Our results indicate that adverse GI events are related not only to the maximum dose but also to the volume of the irradiated medium dose. However, the cut-off value of V35 Gy is 0.5 ml, which is very small and difficult to comply with clinically. On the contrary, the results suggest that it is useful to keep the irradiation range of not only the high-dose range but also the medium-dose range as close to 0 ml as possible in order to reduce adverse GI events above Grade 2. To the best of our knowledge, the present study is the first to report that adverse GI events after stereotactic radiotherapy mainly with IMRT for liver tumors are strongly associated with the medium-dose range, converted to a 2 Gy equivalent dose using the LQ model.

Huang *et al*. reported that in pancreatic cancer, duodenal V25>45% and V35>20% were the most predictive of Grade 3 or higher adverse GI events (12). Yoon *et al*. reported that in HCC, with 30-50 Gy (median 37.5 Gy) at 2-5 Gy (median 3.5 Gy)/fraction, stomach V25 Gy and duodenal V35 Gy were most predictive of Grade 2 or higher GI events in patients treated with 3D-CRT (13). Our study also showed a similar trend in SBRT using mainly IMRT. On the other hand, Sanuki *et al*. and Tsurugai *et al*. reported that the occurrence of GI events was acceptable if GI Dmax and D1cc were followed (8, 9) (Table IV). Doi *et al*. summarized previous reports of adverse GI events in a literature review (5). Our study demonstrated that gastrointestinal D1cc, Dmax, V20, V25, V30, and V35 were all significant predictors of Grade 2 or higher adverse GI events by univariate analysis. Based on these results, it is clear that complying with all of the dose constraints, V35, V30, Dmax, and D1cc, as much as possible is vital. This survey focused on adverse events. The local control rate was poor, but this may be due to the fact that many of the patients were refractory to other treatments (TACE and RFA).

In addition to the limitations of a retrospective study, there were several limitations to this study. First, pre- and post-irradiation gastrointestinal endoscopy was performed only in a subset of patients, which may underestimate Grade 1 adverse GI events, but we believe that Grade 2 or higher symptomatic adverse events can be evaluated. Second, the patient background in this study, including previous treatment, was quite different. In addition, in this study, the stomach, duodenum, and large intestine were evaluated collectively as gastrointestinal PRVs, but essentially, each gastrointestinal tract is considered to have different radiosensitivity. In this study, there were six gastroduodenal adverse events and two colorectal adverse events, but it is difficult to propose an optimal cutoff value for each.

Conclusion

Gastrointestinal V35 was the best predictor of Grade 2 or higher adverse GI events.

Conflicts of Interest

The Authors declare they have no conflicts of interest in relation to this study.

Authors' Contributions

KK and KO conceived the idea of the study. KO developed the statistical analysis plan and conducted statistical analyses. YH and SK contributed to the interpretation of the results. KO drafted the original manuscript. KK supervised the conduct of this study. All Authors reviewed the manuscript draft and revised it critically on intellectual content. All Authors approved the final version of the manuscript.

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