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H. Yoon[1] · D. Oh[2] · H.C. Park[2] · S.W. Kang[4] · Y. Han[2] · D.H. Lim[2] · S.W. Paik[3]

[1] Department of Health Sciences and Technology, School of Medicine & Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul
[2] Department of Radiation Oncology, Samsung Medical Center , Sungkyunkwan University School of Medicine, Seoul
[3] Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul
[4] Department of Radiologic Science, Korea University, Seoul

Predictive factors for gastroduodenal toxicity based on endoscopy following radiotherapy in patients with hepatocellular carcinoma

Radiation therapy (RT) is seldom used for the treatment of hepatocellular carcinoma (HCC) due to a lack of experience and understanding of liver tolerance to RT and technical problems associated with the delivery of RT to part of the liver, as it moves during normal breathing. With recent advances in RT techniques, such as the development of three- or four-dimensional conformal RT and image-guided RT, many institutions have reported their experiences using RT for HCC [8, 9, 12, 15, 17, 19, 20, 21]. The RT dose–response relationship has been well established in HCC [16] and patients with responsive tumors have been shown to have better survival rates [8, 9, 21]. Higher doses of RT are needed for maximal tumor control, but the escalation of RT is limited by organ toxicity. In addition to the liver, gastrointestinal organs near the liver, such as the stomach or duodenum, are the major organs at risk (OAR). Gastroduodenal (GD) tolerance to RT has been investigated in abdominal malignancies [7, 13, 14, 22], but the application of these results to HCC patients requires caution because most HCC patients have liver cirrhosis (LC) and portal hypertension, contributing to the development of GD ulcers [1, 11, 18]. Thus, it is important to investigate predictive factors for GD toxicity in HCC patients.

Previously, we reported that the percentage of GD volume receiving a RT dose of more than 35 Gy (V_{35}) was the most predictive factor for GD toxicity in patients with cirrhosis of the liver [10]. The development of GD toxicity was defined mainly based on patient symptoms. Thereafter, to strengthen our findings, we have tried to perform esophagogastroduodenoscopy (EGD) before and after RT based on the protocol for high-risk patients in whom the target volume is in close proximity to the GD. In the current study, we analyzed the predictive factors for GD toxicity based on EGD findings in HCC patients who were treated with radiotherapy.

Patients and methods

Patients

A total of 445 patients were treated with RT for HCC between October 2008 and December 2010 at our institution. For the current study, we selected 119 patients in whom the GD was located within 2 cm from the planning target volume (PTV). Of the 119 patients, 90 patients who underwent EGD before and after RT were ultimately enrolled in the current study.

Four-dimensional (4D) simulation and RT

All patients underwent 4D-CT simulation. Before simulation, each patient received respiratory training aided by a goggle display, which showed a visual prompting signal based on the prerecorded respiratory cycles for each patient. A CT scan with contrast enhancement was then obtained for the arterial and portal phase during quiet breathing. Images of respiration aided by a goggle display were acquired using the real-time position management (RPM) system (Varian Medical Systems, Palo Alto, CA, USA) to record the respiratory phase. The respiratory phase was divided into ten equal phases with 0% as end inspiration and 50% as end expiration (0–90%). The images of 0, 30, 50, 80% and the portal phase were used to delineate targets and organs at risk (OAR). The portal phase was chosen for dose calculation.

Hyunsik Yoon and Dongryul Oh contributed equally to the article.

Tab. 1 Patient characteristics

Characteristics	Patients n (%)
Age (years)	Median 57 years (range 35–75 years)
Gender	
Male	76 (84%)
Female	14 (16%)
Liver cirrhosis	
Yes	77 (86%)
No	13 (14%)
Child–Pugh classification	
A	78 (87%)
B	12 (13%)
Main PVTT	
Yes	43 (48%)
No	47 (52%)
Interval between previous TACE and RT	
≤17 days	49 (54%)
>17 days	41 (46%)

PVTT portal vein tumor thrombosis, *RT* radiotherapy, *TACE* transcatheter arterial chemoembolization.

Tab. 2 Endoscopic findings and grade of gastroduodenal (*GD*) toxicity related to radiotherapy

GD toxicity related to radiotherapy		Patients n (%)
Endoscopic findings	Duodenitis	15 (17)
	Duodenal ulcer	14 (16)
	Gastritis	14 (16)
	Gastric ulcer	8 (9)
CTCAE grade	0	52 (58)
	1	11 (12)
	2	19 (21)
	3	8 (9)

GD gastroduodenal, *CTCAE* Common Terminology Criteria for Adverse Events.

The gross tumor volumes (GTV), including the main tumors and/or portal vein tumor thrombosis (PVTT), were delineated at each phase and summed to determine the internal target volume (ITV). A 5 mm margin was added to the ITV to create the PTV. RT was delivered as 30–50 Gy (median 37.5 Gy) in 2–5 Gy (median 3.5 Gy) per fraction using a 6, 10, or 15 MV X-ray. All patients were educated for a minimum 2-h fast before simulation and treatment to minimize the variation of stomach volume.

Dosimetric analysis

GD was delineated from the esophagogastric junction to the second portion of the duodenum. The planning OAR volume (PRV), which was obtained from the sum of OAR at each respiratory phase, was chosen for dosimetric analysis in the stomach (S-PRV) and duodenum (D-PRV) to account for organ movement due to respiration. Dose–volume histograms (DVHs) of both S-PRV and D-PRV were calculated. The dosimetric parameters from DVHs were as follows: (1) D_{max}: the maximum dose, (2) $D_{3\ ml}$, $D_{5\ ml}$ and $D_{10\ ml}$: the irradiated dose to 3, 5 and 10 ml of volume, (3) V_{dose}: the percentage of volume receiving more than the irradiated dose and (4) aV_{dose}: the absolute volume receiving more than the irradiated dose. All irradiated doses were converted to the biologically effective dose (BED) as described below.

Mathematical modeling of GD dose

The BED to the GD was calculated by considering the various doses per fraction. First, BED_{10} (α/β=10) was calculated using linear-quadratic model (BED_{10} =n•d•(1+ d/10), where n is the fraction number and d is the daily dose) at each dose. Second, BED_{10} was converted to the 2-Gy equivalent dose ($Gy_{2/10}$ =2-Gy equivalent dose with α/β=10), which was calculated by dividing BED_{10} by (1+ d/10), where d is 2 Gy. For example, a total dose of 30 Gy in 3 Gy per fraction was converted to 32.5 $Gy_{2/10}$.

Endoscopic assessment

One endoscopist and one radiation oncologist reviewed the patients' medical records, endoscopic findings before and after RT, and the RT field. In all patients, EGD was performed at median 2 months (range 1–6 months) after RT. GD toxicity as related to RT was defined as the new development of or the aggravation of endoscopic abnormalities such as an erosive gastroduodenitis or a GD ulcer in close proximity to the RT field following RT. For example, if a new gastric ulcer occurred in the fundus of stomach following RT and only the antrum of the stomach and duodenum were included in the RT field, we did not consider it to be GD toxicity as related to RT. Stomach and duodenum toxicity were evaluated separately and were graded by the Common Toxicity Criteria for Adverse Events, version 3.0.

Statistics

All dosimetric parameters were analyzed using a receiver operating characteristics (ROCs) curve. The area under the curve (AUC) was calculated to determine the best predictive parameters of ≥grade 2 toxicity. The most predictive dosimetric factor and all clinical parameters including gender, age, the presence of LC, Child–Pugh class, the time interval between previous transcatheter arterial chemoembolization (TACE) and RT, the presence of main portal vein tumor thrombosis (PVTT), smoking history, a past history of GD ulcer, and the use of anti-ulcer drug during RT were analyzed by simple and multiple logistic regression. The analyses for the stomach and the duodenum were performed separately. P values less than 0.05 were considered to be statistically significant. SPSS 19.0 was used for analyses.

Results

Patients

The median age of all patients was 57 years (range 35–75 years). In all, 77 patients (86%) had LC and 78 patients (87%) had a classification of Child–Pugh A. The median time interval between RT and previous TACE was 17 days (range 12–782 days). Main PVTT was present in 43 patients (48%). Patient characteristics are summarized in **Tab. 1**. There were 44 (49%) never smokers, 35 (39%) former smokers, and 11 (12%) current smokers. A total of 13 patients had a past history of GD ulcer before RT. Among them, 8 patients used the anti-ulcer drugs during the course of RT.

Endoscopic findings related to RT

Findings in the stomach included erosive gastritis in 14 patients (16%) and gastric ulcers in 8 patients (9%). In comparison, findings in the duodenum included erosive duodenitis in 15 patients (17%)

and duodenal ulcers in 14 patients (16%; **Tab. 2**). The median time to the development of GD toxicity was 3 months (range 1–6 months). Endoscopic findings of GD toxicities related to RT are demonstrated in **Fig. 1**. Grade 2 toxicity developed in 19 patients (21%) and grade 3 toxicity developed in 8 patients (9%; **Tab. 2**). The clinical characteristics of patients who experienced grade 3 toxicity are summarized in **Tab. 3**.

Dosimetric analysis and clinical factors

The results of ROC curve analysis for all dosimetric parameters are shown in **Tab. 4**. For the stomach, V_{25} for S-PRV was the most predictive factor for ≥grade 2 toxicity. The cut-off value was 6.3% and the gastric toxicity rate at 6 months was 2.9% for V_{25} ≤6.3% and 57.1% for V_{25} >6.3% (**Tab. 4**). By multiple logistic regression analysis including the clinical factors, V_{25} was the only significant factor for gastric toxicity (**Tab. 5**).

For the duodenum, ROC analysis showed that V_{35} for D-PRV was the most predictive factor for ≥grade 2 toxicity. The cut-off value was 5.4% and the duodenal toxicity rate at 6 months was 9.4% for V_{35} ≤5.4% and 45.9% for V_{35} >5.4%. (**Tab. 4**) By multiple logistic regression analysis including the clinical factors, V_{35} was the only significant factor for duodenal toxicity (**Tab. 5**).

Discussion

The current study is unique in several ways. First, we selected high-risk patients in whom the GD was in close proximity to the PTV. Second, all GD toxicities were determined by EGD findings. Third, all patients underwent four-dimensional simulation for treatment planning, introducing the concept of PRV for GD to account for organ movement. Our results show that ≥grade 2 GD toxicity occurred in 30% of patients and that the RT dose–volume effect for GD toxicity was shown. V_{25} and V_{35} were the most predictive factors for ≥grade 2 GD toxicity for the stomach and duodenum, respectively.

The GD is the most important dose-limiting factor during RT delivery for

Abstract · Zusammenfassung

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Predictive factors for gastroduodenal toxicity based on endoscopy following radiotherapy in patients with hepatocellular carcinoma

Abstract

Purpose. The aim of this work was to determine predictive factors for gastroduodenal (GD) toxicity in hepatocellular carcinoma (HCC) patients who were treated with radiotherapy (RT).

Patients and methods. A total of 90 HCC patients who underwent esophagogastroduodenoscopy (EGD) before and after RT were enrolled. RT was delivered as 30–50 Gy (median 37.5 Gy) in 2–5 Gy (median 3.5 Gy) per fraction. All endoscopic findings were reviewed and GD toxicities related to RT were graded by the Common Toxicity Criteria for Adverse Events, version 3.0. The predictive factors for the ≥grade 2 GD toxicity were investigated.

Results. Endoscopic findings showed erosive gastritis in 14 patients (16%), gastric ulcers in 8 patients (9%), erosive duodenitis in 15 patients (17%), and duodenal ulcers in 14 patients (16%). Grade 2 toxicity developed in 19 patients (21%) and grade 3 toxicity developed in 8 patients (9%). V_{25} for stomach and V_{35} for duodenum (volume receiving a RT dose of more than x Gy) were the most predictive factors for ≥grade 2 toxicity. The gastric toxicity rate at 6 months was 2.9% for V_{25} ≤6.3% and 57.1% for V_{25} >6.3%. The duodenal toxicity rate at 6 months was 9.4% for V_{35} ≤5.4% and 45.9% for V_{35} >5.4%. By multivariate analysis including the clinical factors, V_{25} for stomach and V_{35} for duodenum were the significant factors.

Conclusion. EGD revealed that GD toxicity is common following RT for HCC. V_{25} for the stomach and V_{35} for the duodenum were the significant factors to predict ≥grade 2 GD toxicity.

Keywords

Hepatocellular carcinoma · Radiotherapy · Gastroduodenal toxicity · Endoscopy, digestive system

Vorhersagefaktoren bei Magen-Darm-Toxizität basierend auf Endoskopie mit darauffolgender Strahlenbehandlung bei Patienten mit Leberzellkrebs

Zusammenfassung

Ziel. Ziel der Studie war es, Vorhersagefaktoren für Magen-Darm-(GD-)Toxizität bei Patienten mit Leberzellkrebs (HCC) zu bestimmen, die eine Strahlenbehandlung (RT) erhalten hatten.

Patienten und Methoden. In die Studie wurden insgesamt 90 HCC-Patienten aufgenommen, die vor und nach einer RT einer Esophagogastroduodenoskopie (EGD) unterzogen wurden. Es wurden RT-Dosen zwischen 30–50 Gy (Median 37,5 Gy) in Einzeldosen zu je 2–5 Gy (Median 3,5 Gy) verabreicht. Alle endoskopischen Ergebnisse wurden überprüft und die GD-Toxizität in Bezug auf die RT wurde entsprechend den Kriterien der „Common Toxicity Criteria for Adverse Events Version 3.0" eingestuft. Untersucht wurde die Vorhersagefaktoren für die GD-Toxizität ≥Stufe 2.

Ergebnisse. Die endoskopischen Befunde zeigten eine erosive Gastritis bei 14 Patienten (16%), Magengeschwüre bei 8 Patienten (9%), erosive Duodenitis bei 15 Patienten (17%) und Duodenalgeschwüre bei 14 Patienten (16%). Eine Stufe-2-Toxizität entwickelte sich bei 19 Patienten (21%), eine Stufe-3-Toxizität bei 8 Patienten (9%). V_{25} für den Magen und V_{35} für den Zwölffingerdarm hatten die höchsten Vorhersagefaktoren bei einer Toxizität ≥Stufe 2. Die Magentoxizitätsrate bei 6 Monaten betrug 2,9% für V_{25} ≤6,3% und 57,1% für V_{25} >6,3%. Die Zwölffingerdarmtoxizitätsrate bei 6 Monaten war 9,4% für V_{35} ≤5,4% und 45,9% für V_{35} >5,4%. Bei multivariaten Analysen inklusive klinischen Faktoren waren V_{25} für den Magen und V_{35} für den Zwölffingerdarm signifikante Faktoren.

Schlussfolgerung. Die EGD hat gezeigt, dass die GD-Toxizität nach einer RT für HCC verbreitet ist. V_{25} für den Magen und V_{35} für den Zwölffingerdarm waren signifikante Faktoren zur Vorhersage einer GD-Toxizität ≥Stufe 2.

Schlüsselwörter

Leberzellkrebs · Strahlentherapie · Magen-Darm-Toxizität · Endoskopie, Verdauungssystem

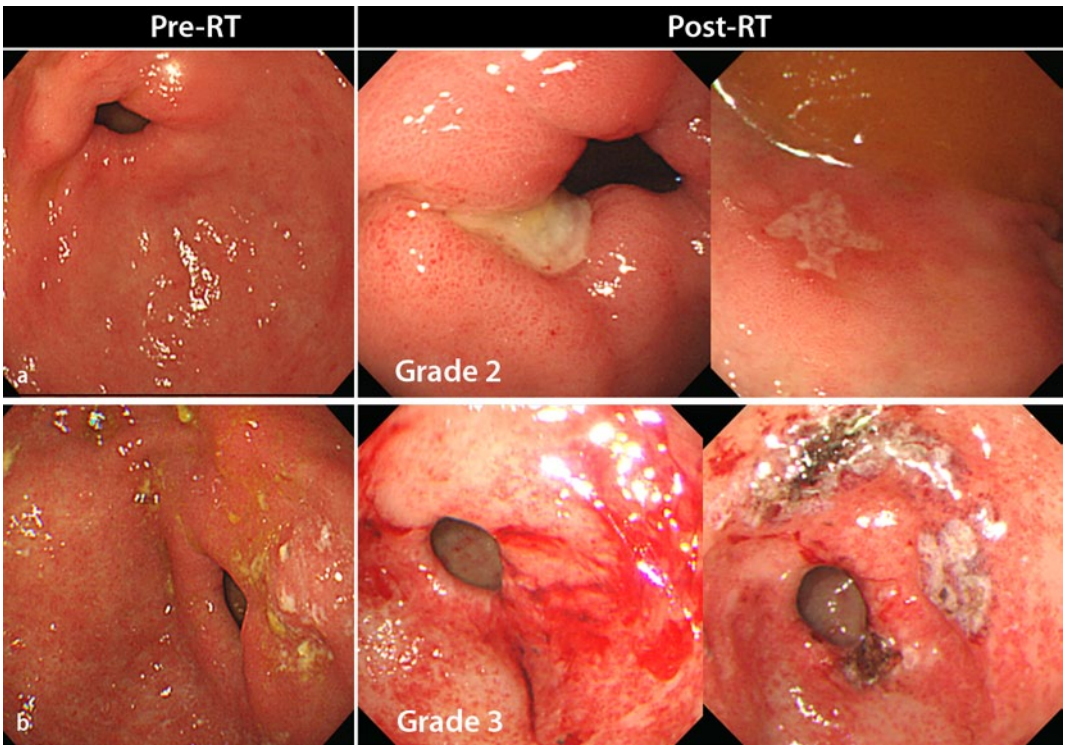

Fig. 1 ◀ Endoscopic findings of gastroduodenal (*GD*) toxicities related to radiotherapy. **a** At 23 days after completion of RT with 35 Gy in 10 fractions, endoscopy showed an approximately 1 cm ulceration with whitish exudate on a pylorus ring and a 5 mm shallow ulceration on a duodenal bulb. Treatment with proton pump inhibitors was initiated. **b** At 107 days after completion of RT with 35 Gy in 10 fractions, endoscopy was performed as the patient had complained of melena. Diffuse mucosal hyperemia with blood oozing on the antrum was observed. Treatment included argon plasma coagulation with two vials of thrombin spray, followed by a transfusion due to the low hemoglobin level of 6.6 g/dl

the treatment of upper abdominal malignancy. The tolerance dose for gastric ulceration was demonstrated by Emami et al. [4]. For the whole stomach, 2/3 of the stomach, and 1/3 of the stomach, 50, 55, and 60 Gy, respectively, were suggested for TD5/5 (the probability of 5% complication within 5 years). In the era of three-dimensional conformal RT (3D-CRT), dose–volume analyses using DVH parameters have been reported. In two recent studies, dosimetric parameters for predicting gastrointestinal toxicity were analyzed in patients with pancreatic cancer treated with CCRT. Huang et al. [7] suggested that limiting the V_{35} of the duodenum to ≤20% may be important for the reduction of grade 3 GI toxicity. Nakamura et al. [14] reported that V_{50} of ≥16 cm^3 may be the best predictor for ≥grade 2 acute GI toxicity.

However, these data may not be applicable for HCC patients because most HCC patients have LC and/or portal hypertension, which are known to be predisposing factors for GD ulcers. The prevalence of GD ulcers in patients with LC is higher than in the general population [1, 11, 18]. Chon et al. [3] showed that the presence of LC was a risk factor for serious GD complications in HCC patients such as bleeding after CCRT. In the present study, Child–Pugh classification B was found to be a risk factor for duodenal toxicity on simple regression analysis. It has been shown that portal hypertension may contribute to an increased risk of GD ulcer as a result of impairment of the gastric mucosal defenses [11]. In an animal experiment, gastric mucosal damage was reduced by portal hypertensive treatment with propranolol [5]. These findings were also observed in endoscopy of cirrhotic patients [6].

Our previous report first showed a dose–volume analysis of GD toxicity in cirrhotic patients with HCC [10]. Grade 2 and 3 GD toxicity was observed in 27.4 and 12.3% of patients, respectively. In addition, our results suggested that V_{35} of <5% could predict ≥grade 3 GD toxicity. Thereafter, GD toxicity has been a concern in HCC patients treated with RT; thus, we tried to perform EGD in high-risk patients to detect the GD toxicity. In the current study, we confirmed the dose–volume effect for GD toxicity, but there were several differences compared to our previous study: GD toxicity was detected based on EGD findings, a BED equivalent of 2 Gy per fraction was used to represent the various doses per fraction, and the concept of PRV was introduced. We found that V_{25} for the stomach and V_{35} for the duodenum were the most predictive factors for ≥grade 2 GD toxicity.

Although the overall incidence of GD toxicity after 3D-CRT has been reported to be between 5.7 and 23.1% [2, 12, 16], there is a lack of data on the evaluation of GD toxicity based on EGD findings. Chon et al. [3] recently reported their EGD findings following CCRT for HCC patients. They showed RT-related gastritis of 40.7%, duodenitis of 34.1%, gastric ulcer of 26.0%, and duodenal ulcer of 16.3%, which were higher values than in our data (**Tab. 2**). The rate of GD bleeding (10.6%) was similar to our results (9%). The use of concurrent chemotherapy, differences in RT volume and prescribed dose, and selection bias for the study population may explain the higher rates of modest complications in the study by Chon et al.

Our study has several limitations. First, we used the concept of PRV as the GD volume in our analysis. However, PRV is not able to represent the true irradiated volume during RT because the stay time of each respiratory phase during the "beam-on" phase of RT could vary. If respiratory-gated RT had been used, the

Tab. 3 Clinical characteristics of patients who experienced grade 3 toxicity

Gender	Child–Pugh Classification	BED (TD/DD)	V_{35} for D-PRV	V_{25} for S-PRV	Time interval between RT and event (days)	Endoscopic findings	Procedure
M/59	A	35.8 (33/3)	37.2	23.5	110	Hemorrhagic GD, GU	APC, thrombin spray
M/68	B	46.7 (40/4)	30.0	4.00	85	Hemorrhagic GD, DU	APC, hypertonic saline inj, thrombin spray
M/64	A	44.0 (44/2)	20.2	72.5	90	Hemorrhagic GD	APC, thrombin spray
M/48	A	35.8 (33/3)	14.7	65.0	108	Hemorrhagic GD	APC, hypertonic saline inj
M/59	A	39.4 (35/3.5)	58.2	3.1	107	Hemorrhagic GD	APC, thrombin spray
M/72	A	35.8 (33/3)	52.7	9.4	126	Hemorrhagic GD, DU	APC, thrombin spray
M/50	A	35.8 (33/3)	37.8	19.6	65	Hemorrhagic GD	APC
M/51	B	35.8 (33/3)	11.4	11.9	25	Hemorrhagic GD, GU	APC, hypertonic saline inj

LC liver cirrhosis, *BED* biologically effective dose with the 2-Gy equivalent dose, *RT* radiation therapy, V_x the percentage of volume receiving more than the irradiated dose x, *D-PRV* duodenal planning organ at risk volume, *S-PRV* gastric planning organ at risk volume, *GD* gastroduodenal, *GU* gastric ulcer, *DU* duodenal ulcer, *APC* argon plasma coagulation, *inj* injection.

Tab. 4 Dosimetric analysis by receiver operating characteristics (*ROCs*) curve

Parameters	S-PRV		D-PRV	
	AUC	p value	AUC	p value
D_{max}	0.765	0.007	0.571	0.240
D_{3ml}	0.812	0.002	0.680	0.023
D_{5ml}	0.825	0.001	0.691	0.026
D_{10ml}	0.821	0.000	0.659	0.034
V_{10}	0.814	0.001	0.596	0.190
V_{15}	0.840	0.004	0.640	0.087
V_{20}	0.852	0.005	0.664	0.046
V_{25}	**0.871**	**0.006**	0.674	0.036
V_{30}	0.846	0.018	0.680	0.039
V_{35}	0.796	0.073	**0.726**	**0.023**
V_{40}	0.531	0.559	0.500	0.434
aV_{10}	0.789	0.006	0.608	0.385
aV_{15}	0.822	0.010	0.636	0.242
aV_{20}	0.841	0.010	0.656	0.181
aV_{25}	0.859	0.012	0.669	0.137
aV_{30}	0.836	0.027	0.677	0.134
aV_{35}	0.792	0.070	0.712	0.136
aV_{40}	0.531	0.318	0.503	0.389

All doses are 2-Gy equivalent normalized doses ($Gy_{2/10}$) with $\alpha/\beta=10$ V_{dose} the percentage of volume receiving more than the indicated dose (%), aV_{dose} absolute volume receiving more than the indicated dose (ml), *PRV* planning organ at risk volume, *S* Stomach, *D* Duodenum, *AUC* the area under the ROC curve, *S-PRV* gastric planning organ at risk volume, *D-PRV* duodenal planning organ at risk volume.

Tab. 5 Logistic regression analysis for clinical and dosimetric factor

	p value	
Parameters	**Simple regression**	**Multiple regression**
Stomach		
Age	0.832	0.590
Gender (male vs. female)	0.795	0.315
Child–Pugh class (B vs. A)	0.411	0.585
Liver cirrhosis (yes vs. no)	0.999	–
Main PVTT (yes vs. no)	0.038	0.082
Time interval between previous TACE and RT (≤17 vs. >17 days)	0.925	0.777
V25 (≤6.3% vs. >6.3%)	<0.001	<0.001
Smoking history (yes vs. no)	0.706	0.664
Past history of ulcer (yes vs. no)	0.365	0.182
The use of anti-ulcer drugs during RT (yes vs. no)	0.999	–
Duodenum		
Age	0.689	0.504
Gender (male vs. female)	0.134	0.241
Child–Pugh class (B vs. A)	0.007	0.146
Liver cirrhosis (yes vs. no)	0.418	–
Main PVTT (yes vs. no)	0.031	0.216
Time interval between previous TACE and RT (≤17 vs. >17 days)	0.615	0.925
V_{35} (≤5.4% vs. >5.4%)	<0.001	0.006
Smoking history (yes vs. no)	0.542	0.170
Past history of ulcer (yes vs. no)	0.418	0.446
The use of anti-ulcer drugs during RT (yes vs. no)	0.969	–

PVTT portal vein tumor thrombosis, *RT* radiotherapy, *TACE* transcatheter arterial chemoembolization.

specific phase could be used for dose–volume analysis. In addition, PRV could not guarantee all variations of organ volume despite of a minimum 2-h fast. Second, we used a 2 Gy equivalent dose per fraction using $\alpha/\beta=10$ because of various dose per fraction as our institutional protocol. Despite this, it may be difficult to generalize our data because of the limitations of the linear-quadratic model in calculating the BED. Third, since this was a retrospective study conducted at one institution, selection bias may influence the determination of the cut-off values for dosimetric factors. If more patients were enrolled, the values might change. Thus, a larger study is necessary to verify our results.

Conclusion

EGD revealed that GD toxicity is a common complication following RT for HCC when the GD is in close proximity to the target volume. It is essential to reduce such GD toxicity in order to improve the quality of life for HCC patients. V_{25}

for the stomach and V_{35} for the duodenum are the predictive factors for GD toxicity.

Corresponding address

H.C. Park, M.D. Ph.D.
Department of Radiation Oncology,
Samsung Medical Center ,
Sungkyunkwan University School of Medicine
50 Irwon-dong, Gangnam-gu, 135-710 Seoul
Korea
rophc@skku.edu

Y. Han, Ph.D.
Department of Radiation Oncology,
Samsung Medical Center ,
Sungkyunkwan University School of Medicine
50 Irwon-dong, Gangnam-gu, 135-710 Seoul
Korea

Conflict of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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