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Comparison of acute gastrointestinal toxicities between 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy including prophylactic regions in chemoradiotherapy with S-1 for pancreatic cancer—importance of dose volume histogram parameters in the stomach as the predictive factors-

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ABSTRACT

The purpose of this study was to compare acute gastrointestinal (GI) toxicities in patients who underwent 3-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) in chemoradiotherapy (CRT) with S-1 including prophylactic regions for pancreatic cancer. We also investigated the predictive factor of acute GI toxicities in dose volume histogram (DVH) parameters. Patients who received CRT with S-1 for pancreatic cancer between January 2014 and March 2021 were included. Radiotherapy (RT) with a total dose of 50-54 Gy was delivered. We examined the differences in the frequencies of acute GI toxicity of grade 2 or higher and DVH parameters of the stomach (ST) and duodenum (DU) between the 3DCRT group and the IMRT group. The RT-related predictive factors of acute GI toxicities were investigated by univariate and multivariate analyses. There were 25 patients in the 3DCRT group and 31 patients in the IMRT group. The frequencies of acute GI toxicity of G2 or higher were 36% in the 3DCRT group and 9.7% in the IMRT group ($p = 0.035$). ST V50 was the most predictive factor ($p = 0.001$), and the incidences of acute GI toxicity of G2 or higher in ST V50 $\geq$ 4.1 cc and $<$ 4.1cc were 43.7% and 7.7%, respectively. ST V40 was also a significant predictive factor of acute GI toxicity ($p = 0.002$). IMRT could reduce acute GI toxicities in CRT with S-1 including prophylactic regions for pancreatic cancer. Acute GI toxicities may be affected by moderate to high doses to the ST.

Keywords: pancreatic cancer; chemoradiotherapy (CRT); IMRT (intensity-modulated radiotherapy); dose volume histogram (DVH); gastrointestinal toxicity

INTRODUCTION

Chemoradiotherapy (CRT) is one of the treatment options for patients with locally advanced pancreatic cancer (LAPC). However, the results of past clinical trials in which chemotherapy alone was compared with CRT for unresectable LAPC were contradictory [1–3]. Moreover, more intensive chemotherapy regimens such as FOLFIRINOX (oxaliplatin, irinotecan, 5-FU and leucovorin) and GnP (nab-Paclitaxel plus gemcitabine) have been more frequently used for unresectable and metastatic cases, and those regimens have shown better treatment results than the results of treatment with gemcitabine (GEM) alone [4, 5]. Therefore, chemotherapy alone has been the mainstay of treatment for unresectable LAPC in current clinical practice.

One of the reasons why chemotherapy alone is preferred for unresectable LAPC is acute gastrointestinal (GI) toxicities such as anorexia, nausea and vomiting induced by irradiation to the stomach (ST) and duodenum (DU) during CRT, leading to considerable loss of quality of life [6]. Although GEM-based or fluorouracil-based concurrent chemotherapy has often been used in CRT for pancreatic cancer, G3-4 nausea and vomiting occurred in about 10–30% of patients in some past studies on CRT with those chemotherapy regimens using 3-dimensional conformal radiotherapy (3DCRT) [1, 2, 7–9]. Regional lymph node metastasis is often detected in patients with pancreatic cancer [10–12], and radiotherapy (RT) field including prophylactic regions may be desirable. On the other hand, since the irradiated volume was shown to be significantly correlated with the development of acute GI toxicities [13], local irradiation has often been performed for pancreatic cancer. Therefore, the range of the optimal RT field for pancreatic cancer remains unclear.

Results of studies on intensity-modulated radiation therapy (IMRT) for pancreatic cancer have been reported [14, 15], and it has become possible to reduce the dose to the ST and DU compared to that with 3DCRT. Recently, fluorouracil-based oral medications such as S-1 and capecitabine have often been used in concomitant chemotherapy of CRT [3, 16–18]. There have been few studies in which it was evaluated in detail whether IMRT including prophylactic regions could reduce acute GI toxicities when used in combination with those oral anticancer drugs. The purpose of this study was to retrospectively analyze the incidences of acute GI toxicities in patients who underwent 3DCRT and IMRT in CRT with S-1 including prophylactic regions for pancreatic cancer. Since the RT-related factors that predict acute GI toxicities have not yet been clearly determined, we also investigated predictive factors of acute GI toxicities.

MATERIALS AND METHODS

Patients and eligibility

Patients with LAPC who underwent CRT with S-1 in our institution between January 2014 and March 2021 were analyzed retrospectively. The main eligibility criteria were as follows: adenocarcinoma confirmed by histological examination for a pancreatic tumor, no distant metastasis before CRT, RT field including the prophylactic regions, adequate oral intake, adequate hematological, hepatic and renal function, no history of surgery for LAPC and no history of RT for an abdominal tumor. This study was approved by the institutional review board (2021-1-291).

Treatment

S-1 was administered orally at a dose of 80 mg/m2 daily on the day during RT. Discontinuation of S-1 administration due to a side effect during treatment was determined by the clinician.

RT was delivered using 10 MV photon beams of a linear accelerator equipped with a multileaf collimator. A daily dose of 1.8–2.0 Gy for five days a week was administered with a total dose of 50–54 Gy. At the time of treatment, RT was performed in condition of hunger that had persisted for at least 3 hours and shallow free breathing. Treatment planning by computed tomography (CT) was performed in all patients. For contouring and dose calculation, the CT images of intravenous contrast medium on an empty ST was acquired under the condition of shallow free breathing, and the slice thickness of the CT scan was 2 mm. Considering respiratory movement of the primary tumor, 10-phases in 4-dimensional computed tomography (4DCT) images using a 16-slice CT machine (SOMATOM Definition, Siemens Healthcare K.K.) were also acquired using a real-time positioning management system (Varian Medical Systems, Palo Alto, CA). Gross tumor volume (GTV) was defined as the primary tumor and metastatic lymph nodes identified on CT. The internal target volume (ITV) for GTV was contoured with reference to the respiratory movement at 4DCT. The clinical target volume (CTV) consisted of CTV_{gross} for GTV and CTV_{pro} for prophylactic region. CTV_{gross} was defined as GTV with ITV plus 5-10-mm margins. Basically, CTV_{pro} included the celiac artery, superior mesenteric artery and paraaortic lymph node region located from the celiac artery to the superior mesenteric artery. Common hepatic and splenic artery lymph node regions were also included in CTV_{pro} as needed. If there was no obvious organ invasion, the overlap between CTV and normal organs was removed. Examples of CTV_{pro} in the pancreas head and body/tail cancer are shown in Fig. 1A–D. The planning target volume (PTV) was defined as CTV plus a 5-mm margin. The ST, DU, liver, kidney and spinal cord was contoured, and contouring of the ST and DU was based on the report by Jabbour *et al.* [19]. The planning organs at risk volume (PRV) of the ST/duodenum and PRV of the spinal cord were defined as 5-mm and 3-mm margins of the normal organ, respectively.

In 3DCRT, four or five field techniques were performed by daily image guidance with kv X-ray on Clinac 23EX (Varian Medical Systems, Palo Alto, CA, USA), and the reference point for the prescribed dose was put at the center of the PTV. RT planning was performed by ECLIPSE (Varian Medical Systems, Palo Alto, CA) with an analytical anisotropic algorithm. The dose constraints of organs at risk were as follows: liver V30Gy $<$ 30%; kidney V18Gy $<$ 35%; spinal cord (PRV) Dmax $<$ 45Gy. In IMRT, volumetric modulated arc therapy (VMAT) by daily image guidance with cone beam CT was performed on Versa HD (Elekta Oncology Systems, Crawley, UK). RT planning was performed by Monaco (Elekta Oncology Systems, Crawley, UK) with a Monte Carlo algorithm. The dose prescription of the VMAT plan was set as D95 (95% of volume covered by the prescribed dose) for PTV-PRV to protect the dose constraints of the ST and duodenum (DU). Regarding the overlap between PTV and PRV, the percentage of the volume covered by 95% and 90% of the prescribed dose was adjusted to be $\geq$ 50% and $\geq$ 95%, respectively. Dose constraints of organs at risk were as follows: ST/DU V52.5Gy $<$ 0.1cc, V50Gy $<$ 1cc, V45Gy $<$ 30cc, V40Gy $<$ 50cc; ST/DU (PRV) V55Gy $<$ 0.1cc, V52.5Gy $<$ 1.0cc; liver V30Gy $<$ 30%; kidney $<$ 35%; spinal cord

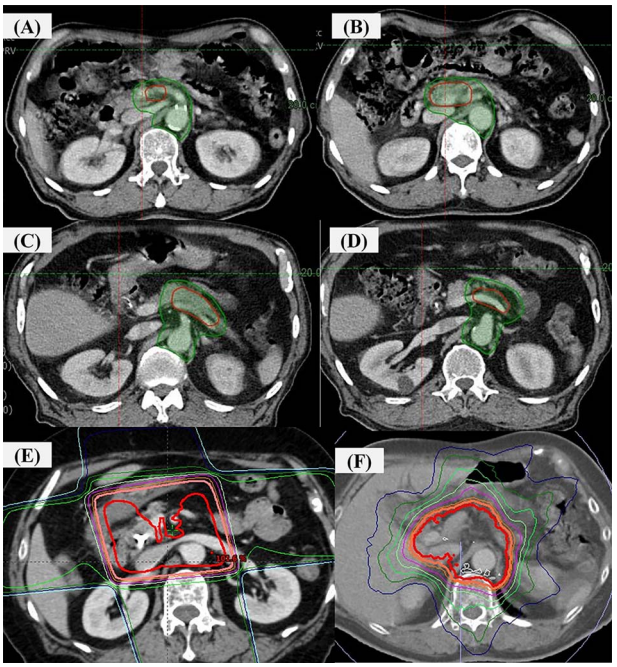

Fig. 1. Examples of contouring (red line: gross target volume; green line: CTV) of prophylactic regions for carcinoma of the pancreas head (A, B) and the pancreas body or tail (C, D) and the dose distributions in 3DCRT (E) and IMRT (F). The dose distributions in Fig. 1(E) and Fig. 1(F) are not for the same patient

(PRV) Dmax < 45Gy. Dose distributions of 3DCRT and IMRT are shown in Fig 1. E and F, respectively.

Toxicity assessment

Acute toxicities were defined as symptoms that occurred from the start of CCRT to 14 days after the completion of CRT. The acute toxicities were evaluated according to Common Terminology Criteria for Adverse Events, Version 5.0. GI toxicities were defined as acute toxicities related to the ST and DU such as anorexia, nausea and vomiting. The worst grade among those was defined as the grade of GI toxicity.

Statistical analysis

Differences in dose volume histogram (DVH) parameters of the PTV, ST, DU, liver and kidney between the 3DCRT group and the IMRT group were investigated by the Mann-Whitney U test. The correlations between PTV and DVH parameters of the ST and DU were also examined using Spearman's rank correlation coefficient in the 3DCRT group and the IMRT group. Regarding acute GI toxicities, we examined whether there was a significant difference in grade 2 or higher between the 3DCRT and IMRT groups by Fisher's exact test.

We investigated DVH parameters of the ST and DU related to GI toxicity of grade 2 or higher by the Mann-Whitney U test. After that, a cutoff value in the DVH parameters of the ST and DU with a p value < 0.10 was determined by the receiver operating characteristic (ROC) curve to predict GI toxicity of G2 or higher. Based on the cutoff value, the odds ratios of each factor were calculated using logistic regression analysis. We also evaluated the differences of GI toxicity by predictive factors other than the DVH parameters of the ST and DU (age, gender, tumor location, induction chemotherapy, CA19-9 value, GTV volume and PTV volume). Continuous variables were analyzed using the Mann-Whitney U test. Dichotomous variables were analyzed using Fisher's exact test. Multivariate analysis was performed by the logistic regression analysis using factors with a p value < 0.05.

All statistical tests were two-sided, and statistical significance was defined as a value of $p < 0.05$. Statistical analysis was performed using JMP® 15 (SAS Institute, Cary, NC, USA).

RESULTS

Fifty-six LAPC patients without distant metastasis who received CRT were analyzed. Patient characteristics are shown in Table 1. The median GTV and median PTV were 22.9 cc (interquartile range [IQR], 12.2–36.7 cc) and 253.5 cc (IQR, 204.3–294.7 cc), respectively. There were significant differences in the content of induction chemotherapy, RT dose and PTV between the 3DCRT and IMRT groups.

A comparison of DVH parameters of the PTV, ST and DU between the 3DCRT and IMRT groups is shown in Table 2. The values of ST V50, V40 and V30 and DU V50 were lower in the IMRT group than in the 3DCRT group. The dose coverage for the PTV was more sufficient in the IMRT group than in the 3DCRT group. There was no significant difference in liver V30 and kidney V18 between the two groups. The correlations between PTV and DVH parameters of ST and DU in the 3DCRT group and the IMRT group are shown in Fig. 2 and Fig. 3. ST V30 and ST V40 in the 3DCRT group were correlated with PTV volume. Although RT was discontinued due to Herpes zoster in one patient in the 3DCRT group, CRT was completed in the other patients. The patient who suffered from Herpes zoster was also included in the present study because RT was discontinued at 44 Gy in 22 fractions. Administration of S-1 was discontinued in four patients (16%) in the 3DCRT group and in one patient (3.3%) in the IMRT group ($p = 0.16$). The results of acute GI were shown in Table 3. We confirmed that there was no major problem with oral intake before CRT in all patients. The frequencies of acute GI toxicities of grade 2 or higher in the 3DCRT and IMRT group were 36% (nine patients) and 9.7% (three patients), respectively ($p = 0.024$). The results for clinical and RT-related parameters associated with acute GI toxicities are shown in Table 4. ST V50, ST V40, ST V30, ST V20, ST V10, DU mean dose and DU V50 were identified in univariate analysis as significant predictive factors for acute GI toxicities of grade 2 or higher. There were no significant differences in other predictive factors including GTV and PTV. The cutoff values and areas under curves using ROC curves in RT-related factors of $p < 0.10$ (ST V50, ST V40, ST V30, ST V20, ST V10, DUmean and DU50) are shown in Table 4. We confirmed that there were significant differences in acute GI toxicity of grade 2 or higher using those cutoff values. The DVH parameters of the ST were significantly correlated with each other (Spearman's correlation coefficient, $p < 0.05$). The DVH parameters of the DU were significantly correlated with each other. Therefore, multivariate analysis was performed for ST V50 and DU V50. As a result, ST V50 was the only

Table 1. Patient characteristics

Characteristics	3DCRT	IMRT	P value
Age (year) (Median, IQR)	69 (60–73)	69 (63–72)	0.875
Gender			0.344
Male	13	20	
Female	12	11	
Tumor location			0.444
Head	17	18	
Body/Tail	8	13	
Resectability			0.096
BR	4	11	
UR-LA	21	20	
Tumor size (cm) (Median, IQR)	3.4 (2.95–4.35)	2.9 (2.7–3.7)	0.097
CA19-9 before RT (U/ml) (Median, IQR)	54.5 (13.9–168.0)	31.9 (11.9–59.3)	0.156
Induction chemotherapy			**0.039**
None	5	1	
GEM+nabPTX	17	28	
FOLFININOX	2	2	
GEM+S-1	1	0	
Radiation dose			**0.001**
50.4Gy/28fr	8	2	
50Gy/25fr	12	29	
54Gy/30fr	5	0	
GTV (cc) (Median, IQR)	23.3 (8.0–44.7)	22.4 (14.5–36.2)	0.767
PTV (cc) (Median, IQR)	267.7 (207.6–356.9)	242.1 (199.7–246.6)	**0.041**

Abbreviations: 3DCRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; BR = borderline resectable; UR-LA = unresectable locally advanced; GTV = gross target volume, PTV = planning target volume; IQR = interquartile range.

prognostic factor of acute GI toxicities ($p = 0.004$). Similar results were obtained for other ST parameters (ST V40, V30, V20 and V10).

DISCUSSION

Acute GI toxicities caused during CRT may affect the patient's quality of life and have been one of the main problems to be solved in CRT for pancreatic cancer. It is expected that additional treatment such as chemotherapy and surgery would be performed in most cases after CRT for LAPC. Since pancreatic cancer has the characteristic of rapid progression, it may be important to smoothly perform additional treatment after CRT. Naumann *et al.* reported that patients with weight loss during CRT for pancreatic cancer had higher rates of grade 2 nausea and that weight loss during CRT was associated with overall survival [20]. Therefore, we focused mainly on acute GI toxicities of grade 2 or higher in the present study, although past studies reported GI toxicities of grades 3 and 4 were observed in some patients in past studies [1.2.7.9]. We found: (i) that IMRT including the prophylactic regions was well tolerable in CRT with fluorouracil-based oral medications for pancreatic cancer, and (ii) that DVH parameters of the ST were the significant factors to predict the acute GI toxicities.

In the present study, the frequencies of acute GI toxicity of G2 or higher were 36% in the 3DCRT group and 9.7% in the IMRT group. The results of a systematic review of the past data for 3DCRT and IMRT showed that the frequency of acute GI toxicity of grade 3 or higher was significantly lower in the IMRT group than in the 3DCRT group [6]. Although there have been a few studies in which the differences in acute GI toxicities of grade 2 or higher or grade 3 or higher between 3DCRT and IMRT were directly evaluated, the results of those studies are shown in Table 6 [21–23]. They reported that IMRT was able to reduce acute GI toxicities with or without including prophylactic regions, and similar results were obtained in the present study. Although the PTV was smaller in the IMRT group than in the 3DCRT group in the present study, we also demonstrated that IMRT was able to reduce the dose to the ST and DU while maintaining a sufficient dose coverage. Moreover, the volumes irradiated to the ST and DU at IMRT were quite lower than those at the dose constraints of the present study. Therefore, it was shown that IMRT including prophylactic regions for pancreatic cancer could be tolerated well.

S-1 was used for concurrent chemotherapy in the present study. Compared to past reports on CRT with S-1, there were few cases of acute GI toxicity of grade 3 or higher in both 3DCRT and IMRT in the present study as shown in Table 5 [17, 24, 25]. The main reason for this difference might be that the use of 4DCT contributed to the reduction of PTV with consideration of respiratory movements for each patient in the present study. The median PTV was 240 cc in the study of Ikeda *et al.* with RT field including only local region [17], whereas the median PTV was 253.5 cc in the present study with RT field including local and prophylactic regions using 4DCT at RT planning. There was also a report showing that the use of 4DCT reduced acute GI toxicities [23]. It has been reported that capecitabine had better treatment results than GEM as concurrent chemotherapy of CRT [16], and good treatment results were obtained in CRT with S-1 [18]. Therefore, we believe that

Table 2. Comparison of DVH parameters of the PTV, ST and DU between the 3DCRT and IMRT groups

Factor (Median, IQR)	3DCRT	IMRT	P value
ST mean dose (Gy)	21.3 (16.7–25.7)	17.8 (13.6–22.8)	0.051
ST V50 (cc)	7.7 (0.2–12.3)	0.1 (0–0.2)	< **0.001**
ST V40 (cc)	28.5 (15.5–38.4)	12.5 (6.7–23.4)	**0.006**
ST V30 (cc)	50.9 (20.9–71.6)	34.1 (18.8–51)	0.082
ST V20 (cc)	91.4 (37.5–127.8)	69.8 (47.2–107.8)	0.382
ST V10 (cc)	123.4 (72.4–153.1)	119.6 (77.5–141.6)	0.581
DU mean dose (Gy)	31.7 (24.6–37.6)	27.0 (16.8–33.4)	0.063
DU V50 (cc)	3.1 (0.1–14.3)	0.1 (0–0.1)	**0.001**
DU V40 (cc)	12.6 (6.7–31.2)	12.8 (4.5–20.1)	0.448
DU V30 (cc)	20.5 (11.7–39.1)	22.9 (16.9–31.8)	0.902
DU V20 (cc)	34.1 (19.6–50.7)	35.5 (21.5–46.8)	0.902
DU V10 (cc)	38.5 (23.8–53.0)	40.9 (28.9–53.4)	0.604
PTV mean dose (%)	99.2 (97.1–99.8)	101.7 (101.3–102.0)	< **0.001**
PTV D95% (%)	94.8 (92.1–95.9)	96.8 (95.8–98.2)	< **0.001**

Abbreviations: 3DCRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; ST = stomach; DU = duodenum; PTV = planning target volume; IQR = interquartile range.

Table 3. Results of acute GI toxicities. The frequencies of acute GI toxicities of grade 2 or higher in the 3DCRT group were higher than those in the IMRT group

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Overall					
3DCRT	6 (24%)	10 (40%)	8 (32%)	1 (4%)	0 (0%)
IMRT	8 (25.8%)	20 (64.5%)	2 (6.5%)	1 (3.2%)	0 (0%)
Anorexia					
3DCRT	6 (24%)	12 (48%)	6 (24%)	1 (4%)	0 (0%)
IMRT	11 (35.5%)	19 (61.3%)	0 (0%)	1 (3.2%)	0(0%)
Nausea					
3DCRT	12 (48%)	8 (32%)	4 (16%)	1 (4%)	0 (0%)
IMRT	21 (67.7%)	7 (22.6%)	2 (6.5%)	1 (3.2%)	0 (0%)
Vomiting					
3DCRT	20 (80%)	4 (16%)	1 (4%)	0 (0%)	0 (0%)
IMRT	30 (96.8%)	0 (0%)	1 (3.2%)	0 (0%)	0 (0%)

Abbreviations: 3DCRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy.

the results of our study will contribute to the establishment of CRT with oral fluorouracil-based chemotherapy for pancreatic cancer.

We also investigated the relationship between acute GI toxicities and dose to the ST and DU. We found that there were significant differences in acute GI toxicities in DVH parameters of the ST. The results of a small number of studies in which the doses to the ST and DU in acute GI toxicities were evaluated using conventional fractionated RT are shown in Table 6. Nakamura *et al.* reported that ST V50 was a strong predictive factor [26], and the incidence of GI toxicity of grade 2 or higher at the cutoff value in their study was similar to that in the present study. Based on those results, the volume of high doses to the ST should be reduced as much as possible. On the other hand, Holyoake *et al.* reported that the volume of the ST that was irradiated with a moderately high dose (35–45 Gy) was a predictive factor of acute GI toxicity [27]. ST V40 and ST V30 were also identified as predictive factors in the present study, and a moderate dose to the ST was also shown to be a predictive factor of acute GI toxicities in a study on hypofractionation RT for pancreatic cancer [28]. Therefore, even moderate doses to the ST may affect acute GI toxicities. In the present study, we also have shown that IMRT could reduce moderate dose to ST regardless of PTV volume. Although the volume of low dose to the ST was also affected with acute GI toxicities in the present study, the volume of low dose irradiation may vary greatly depending on the daily position of the ST. Therefore, it would be difficult to use the volume of low dose to the ST as an index of acute GI toxicities. Recently, there have been reports on the benefits of dose escalation for pancreatic cancer [14, 15, 23]. Administration of a high dose inside the tumor using IMRT by means of a simultaneous integrated boost may be effective [29]. Although it was not clear by multivariate analysis in the present study, DU mean and DU V50 were predictive factors among the DU parameters. Although duodenal parameters were not shown as prognostic factors of acute toxicities in other reports, high-dose

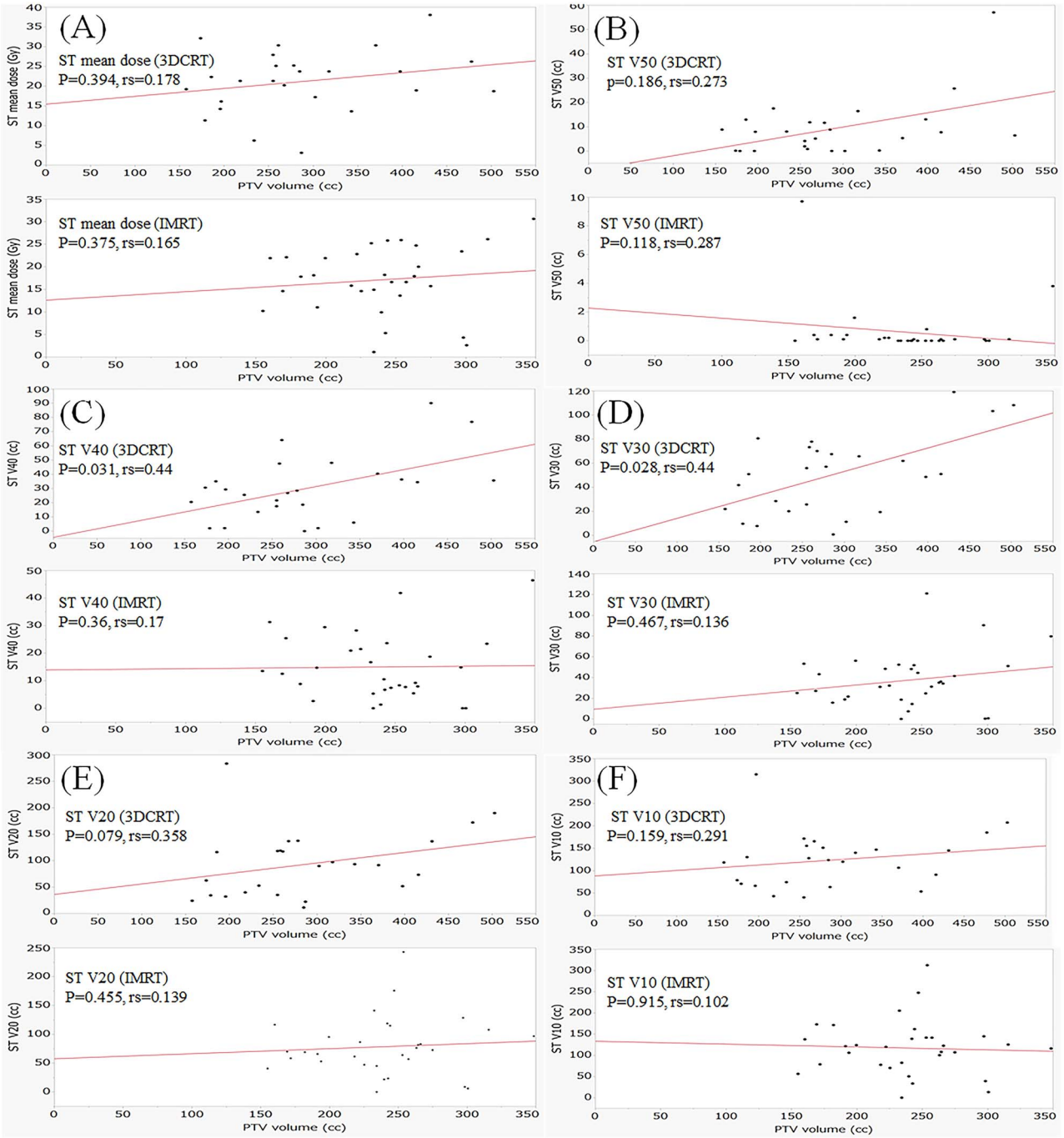

Fig. 2. The results of correlations between PTV and DVH parameters of the ST (A: ST mean dose, B: ST V50, C: ST V40, D: ST V30, E: ST V20; F: ST V10). The results of 3DCRT and IMRT are shown above and below each figure. ST V30 and ST V40 in the 3DCRT group were correlated with PTV.

irradiation to the DU may cause a duodenal ulcer as a late toxicity [26, 30]. Late GI toxicities should be considered more than acute GI toxicities in RT planning for pancreatic cancer. Nakamura *et al.* reported that V50 of the ST and DU (33 cm^3 or more) was the best predictor of upper GI bleeding [26], and Kelly *et al.* reported that DU V55 of more than 1 cm^3 was an important predictor of late toxicity of grade 2 or higher [30]. Although late GI toxicities were not evaluated in the present study, the ST and DU dose constraint of our study were determined more carefully with the priority of preventing late GI toxicities referring to those past studies. At IMRT planning for pancreatic cancer, it may

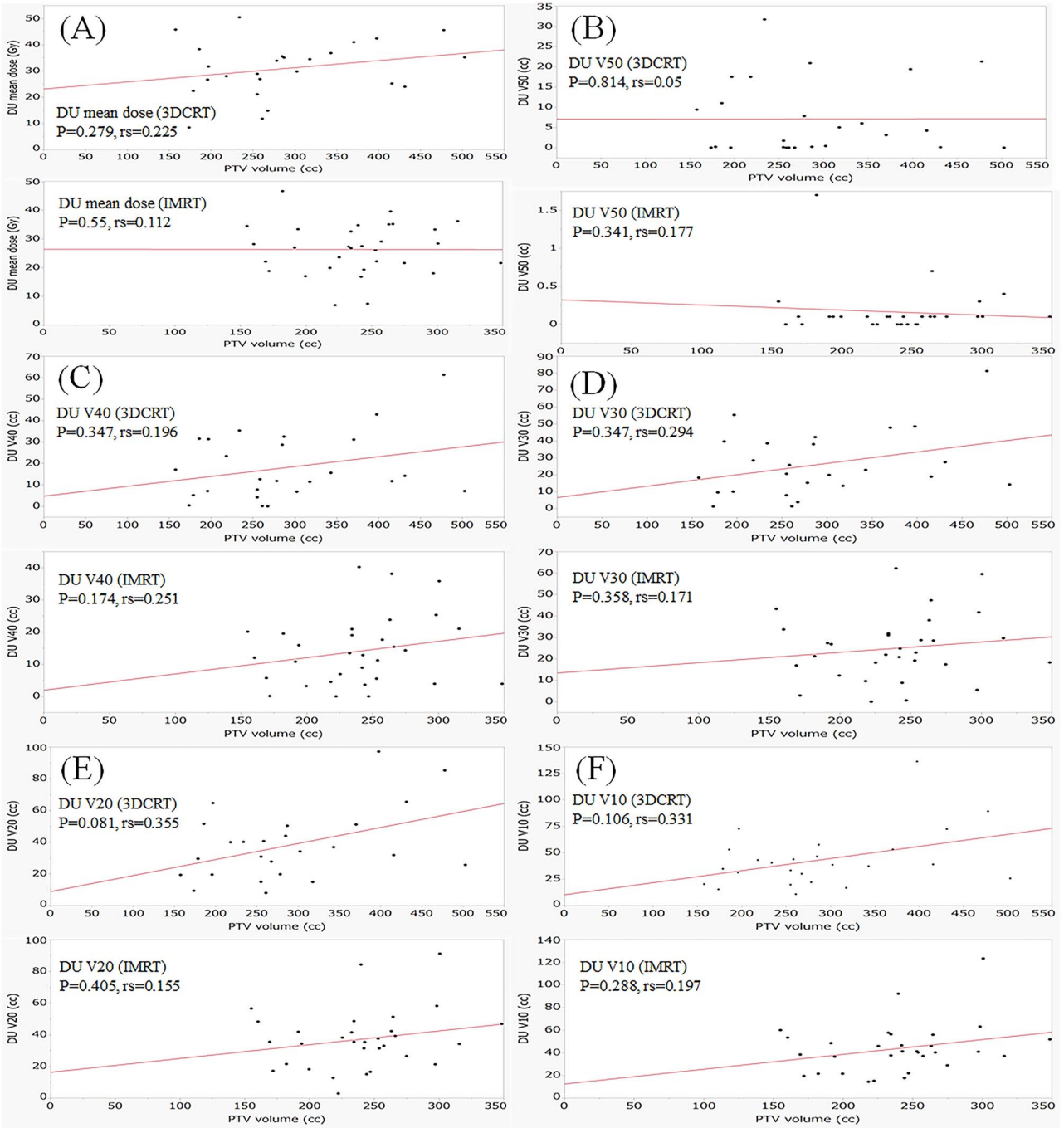

Fig. 3. The results of the correlations between PTV and DVH parameters of the DU (A: DU mean dose, B: DU V50, C: DU V40, D: DU V30, E: DU V20; F: DU V10). The results of 3DCRT and IMRT are shown above and below each figure There were no significant correlations between PTV and DVH parameters in either 3DCRT or IMRT.

be preferable to meet our dose constraints about acute GI toxicities as much as possible while avoiding the high-dose irradiation of more than 50 Gy to ST and DU to prevent late GI toxicities.

There were some limitations in the present study. First, acute GI toxicity might have been underestimated because of the retrospective analysis in the present study. Upper GI endoscopy was not performed routinely in the present study. Although it was not possible to evaluate weight loss and detailed oral intake in the present study, CRT was completed without the need of intravenous drip infusion in most patients. Second, there were differences in induction chemotherapy and RT dose between the 3DCRT group and the IMRT group. Some studies have shown that the response rate to intensive chemotherapy regimens

Table 4. RT-related parameters associated with acute gastrointestinal toxicities

Factor	G0-1 (Median, IQR)	G2-4 (Median, IQR)	UA p value	MA p value	Cutoff value	Incidence rate of ≥ G2	AUC	OR
ST mean dose (Gy)	18.2 (13.8–23.7)	21.8 (18–26.2)	0.119					
ST V50 (cc)	0.1 (0–1.83)	8.35 (1.33–15.5)	**0.001**	**0.001**	4.1	Below: 7.7% Above: 52.9%	0.800	13.5 (95%CI, 2.97–61.4)
ST V40 (cc)	14.8 (6.18–27.9)	32.2 (20.8–38.4)	**0.011**	**0.002**	20.5	Below: 7.1% Above: 35.7%	0.741	7.22 (95%CI, 1.41–37.0)
ST V30 (cc)	34.6 (19.5–52.2)	60.7 (29.1–97.5)	**0.034**	**0.018**	50.8	Below: 8.8% Above: 40.9%	0.701	7.15 (95%CI, 1.66-30.8)
ST V20 (cc)	67.8 (41.8–96.4)	116.6 (76–163.1)	**0.030**	**0.023**	97.1	Below: 8.1% Above: 47.4%	0.706	10.2 (95%CI,2.31–45.0)
ST V10 (cc)	107.4 (70.2–141.6)	142.4 (125.9–181.5)	**0.011**	**0.028**	125.1	Below: 6.5% Above: 40%	0.741	9.67 (95%CI, 1.87–49.9)
DU mean dose (Gy)	27.2 (21.6–34.4)	34.9 (25.9–43.8)	**0.037**	0.204	31.7	Below: 9.1% Above: 39.1%	0.699	6.42 (95%CI, 1.50–27.5)
DU V50 (cc)	0.1 (0–0.28)	1.7 (0.2–10.6)	**0.020**	0.299	0.3	Below: 8.3% Above: 45%	0.716	9.00 (95%CI, 2.06–39.3)
DU V40 (cc)	11.9 (4.68–20.7)	18.3 (8.7–29.8)	0.156					
DU V30 (cc)	22.4 (10.6–33.2)	24.3 (15.2–41.2)	0.442					
DU V20 (cc)	35.5 (22.6–43.5)	32.5 (19.9–63.0)	0.873					
DU V10 (cc)	40.4 (30.3–50.251.0)	35.2 (20.5–70.0)	0.764					

Abbreviations: RT = radiotherapy; ST = stomach; DU = duodenum; UA = Univariate analysis; MA = multivariate analysis; IQR = interquartile range; AUC = area under curve; OR = odds ratio.

Table 5. Comparison of incidences of acute GI toxicities of G3-4 in CRT with S-1 between the present study and other studies

Author	RT dose	RT field	RT technique	Anorexia	Nausea	Vomiting	Diarrhea
Kim *et al.* (2009) [23]	50.4Gy/28fr	P+L	3DCRT	20%	4%	4%	0%
Sudo *et al.* (2011) [24]	50.4Gy/28fr	L	3DCRT	24%	12%	0%	0%
Ikeda *et al.* (2012) [17]	50.4Gy/28fr	L	3DCRT	7%	5%	3%	0%
Present study	50–54Gy	P+L	3DCRT	4%	4%	0%	0%
			IMRT	3.2%	3.2%	0%	0%

Abbreviations: RT = radiotherapy; P = prophylactic; L = local: 3DCRT = 3-dimensional conformal radiotherapy; IMRT = intensity modulated radiotherapy.

such as FOLFIRINOX and GnP was higher than that to GEM for LAPC [4, 5], and patients who received FOLFININOX and GnP may have had a good general condition. Therefore, although it was possible that the disease stability in the IMRT group was better than that in 3DCRT group, there was no major problem with oral intake before CRT in all patients, and there was no significant difference between acute GI toxicity in that in patients who received induction chemotherapy and that in patients who did not receive induction chemotherapy. Third, there was also a difference in PTV between the 3DCRT group and the IMRT group. However, PTV was not a predictive factor for acute GI toxicities in univariate analysis.

In conclusion, the incidence of (GI) toxicity was significantly reduced in the IMRT group, suggesting that CRT with a combination of S-1 including the prophylactic regions for pancreatic cancer was tolerable. The incidence of acute GI toxicity may be related to a moderate to high dose to the ST.

Table 6. Comparison of the acute GI toxicities in CRT between the present study and other studies

3DCRT vs IMRT

Author	n	Setting	Concurrent chemotherapy	RT technique	Dose	RT Field	Toxicity	Predictive factor	
Yovino *et al.* (2011) [20]	46	Adjuvant	5-FU	3DCRT	50.4–59.4Gy	P+L	2–17% (GI ≥G3)	IMRT	
				IMRT			0–4%(GI ≥ G3)		
Prasad *et al.* (2016) [21]	205	Definitive	5-FU/cape, GEM-based	3DCRT	50.4Gy/28fr	P+L	34% (GI ≥ G2)	IMRT	
				IMRT(SIB)	56Gy/28fr		16% (GI ≥ G2)		
Colbert *et al.* (2017) [22]	154	Definitive	5-FU/cape, GEM-based	3DCRT	50.4Gy/28fr	L	27% (GI ≥ G2)	No factor	
				IMRT	63–70Gy		12% (GI ≥ G2)		
Radiation-related parameter									
Author	n	Setting	Concurrent chemotherapy	RTtech-nique	Dose	RT Field	Toxicity	Predictive factor	
Nakamura *et al.* (2012) [25]	40	Definitive	GEM	3DCRT+ IMRTboost	54Gy/30fr	L	33% (GI ≥ G2)	Stomach V50 < 16cm2: 9% ≥ 16cm2: 61%	
Holyoake *et al.* (2018) [26]	91	Definitive	GEM+CDDP, NFV, GEM,Cape	3DCRT	59.4Gy/33fr	P+L	38.1%(GI ≥ G2)	Stomach V35	
					50.4Gy/28fr	L	25.7%(GI ≥G2)	GI G0-1: 30.9cm2 GI ≥G2: 39.4cm2	
Present study	56	Definitive	S-1	3DCRT	50.4–54Gy	P+L	36%(GI ≥G2)	Stomach V50	Stomach V40
				IMRT	50–5.4Gy		9.7%(GI ≥G2)	< 6.1cm2: 7.7% ≥ 6.1cm2: 52.7%	< 20.5cm2: 7.1% ≥20.5cm2: 35.7%

Abbreviations: GI = gastrointestinal; CRT = chemoradiotherapy; 5-FU = 5-fluorouracil; GEM = gemcitabine; CDDP = cisplatin; NFV = Nelfinavir; 3DCRT = 3-dimensional radiotherapy; IMRT = intensity-modulated radiotherapy; SIB = simultaneous integrated boost; RT = radiotherapy; GEM = gemcitabine; CDDP = cisplatin; NFV = Nelfinavir; P = prophylactic; L = local.

CONFLICT OF INTEREST

All authors declare no conflict of interest related to this study. There are no financial supports from any company for this study, and there are no conflicts of interests to declare.

PRESENTATION AT A CONFERENCE

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REFERENCES

1. Chauffert B, Mornex F, Bonnetain F et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol* 2008;19:1592–9.
2. Loehrer PJ Sr, Feng Y, Cardenes H et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an eastern cooperative oncology group trial. *J Clin Oncol* 2011;29:4105–12.
3. Hammel P, Huguet F, van Laethem JL et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without Erlotinib: the LAP07 randomized clinical trial. *JAMA* 2016;315:1844–53.

4. Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–25.
5. Von Hoff DD, Ervin T, Arena FP et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–703.
6. Bittner MI, Grosu AL, Brunner TB. Comparison of toxicity after IMRT and 3D-conformal radiotherapy for patients with pancreatic cancer - a systematic review. *Radiother Oncol* 2015;114:117–21.
7. Okusaka T, Ito Y, Furuse J et al. Current status of chemoradiotherapy for locally advanced pancreatic cancer in Japan. *Int J Clin Oncol* 2008;13:127–31.
8. Huang J, Robertson JM, Margolis J, Balaraman S, Gustafson G, Khilanani P, Nadeau L, Jury R, McIntosh B. Long-term results of full-dose gemcitabine with radiation therapy compared to 5-fluorouracil with radiation therapy for locally advanced pancreas cancer. *Radiother Oncol* 2011; 99:114–9.
9. Goldstein D, Van Hazel G, Walpole E et al. Gemcitabine with a specific conformal 3D 5FU radiochemotherapy technique is safe and effective in the definitive management of locally advanced pancreatic cancer. *Br J Cancer* 2007;97:464–71.
10. Sohn TA, Yeo CJ, Cameron JL et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000;4:567–79.
11. Shimada K, Sakamoto Y, Sano T, Kosuge T. Prognostic factors after distal pancreatectomy with extended lymphadenectomy for invasive pancreatic adenocarcinoma of the body and tail. *Surgery* 2006;139:288–95.
12. Kayahara M, Nagakawa T, Ohta T et al. Analysis of paraaortic lymph node involvement in pancreatic carcinoma: a significant indication for surgery? *Cancer* 1999;85:583–90.
13. Ito Y, Okusaka T, Kagami Y et al. Evaluation of acute intestinal toxicity in relation to the volume of irradiated small bowel in patients treated with concurrent weekly gemcitabine and radiotherapy for locally advanced pancreatic cancer. *Anticancer Res* 2006;26:3755–9.
14. Krishnan S, Chadha AS, Suh Y et al. Focal radiation therapy dose escalation improves overall survival in locally advanced pancreatic cancer patients receiving induction chemotherapy and consolidative chemoradiation. *Int J Radiat Oncol Biol Phys* 2016;94:755–65.
15. Ben-Josef E, Schipper M, Francis IR et al. A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2012;84:1166–71.
16. Mukherjee S, Hurt CN, Bridgewater J et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol* 2013;14:317–26.
17. Ikeda M, Ioka T, Ito Y et al. A multicenter phase II trial of S-1 with concurrent radiation therapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2013;85:163–9.
18. Ioka T, Furuse J, Fukutomi A et al. Randomized phase II study of chemoradiotherapy with versus without induction chemotherapy for locally advanced pancreatic cancer: Japan clinical oncology group trial, JCOG1106. *Jpn J Clin Oncol* 2021;51:235–43.
19. Jabbour SK, Hashem SA, Bosch W et al. Upper abdominal normal organ contouring guidelines and atlas: a radiation therapy oncology group consensus. *Pract Radiat Oncol* 2014;4:82–9.
20. Naumann P, Eberlein J, Farnia B et al. Continued weight loss and sarcopenia predict poor outcomes in locally advanced pancreatic cancer treated with chemoradiation. *Cancers (Basel)* 2019;11:709.
21. Yovino S, Poppe M, Jabbour S et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. *Int J Radiat Oncol Biol Phys* 2011;79:158–62.
22. Prasad S, Cambridge L, Huguet F et al. Intensity modulated radiation therapy reduces gastrointestinal toxicity in locally advanced pancreas cancer. *Pract Radiat Oncol* 2016;6:78–85.
23. Colbert LE, Moningi S, Chadha A et al. Dose escalation with an IMRT technique in 15 to 28 fractions is better tolerated than standard doses of 3DCRT for LAPC. *Adv Radiat Oncol* 2017;2:403–15.
24. Kim HM, Bang S, Park JY et al. Phase II trial of S-1 and concurrent radiotherapy in patients with locally advanced pancreatic cancer. *Cancer Chemother Pharmacol* 2009;63:535–41.
25. Sudo K, Yamaguchi T, Ishihara T et al. Phase II study of oral S-1 and concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2011;80:119–25.
26. Nakamura A, Shibuya K, Matsuo Y et al. Analysis of dosimetric parameters associated with acute gastrointestinal toxicity and upper gastrointestinal bleeding in locally advanced pancreatic cancer patients treated with gemcitabine-based concurrent chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2012;84:369–75.
27. Holyoake DLP, Warren DR, Hurt C et al. Stomach dose-volume predicts acute gastrointestinal toxicity in chemoradiotherapy for locally advanced pancreatic cancer. *Clin Oncol (R Coll Radiol)* 2018;30:418–26.
28. Cattaneo GM, Passoni P, Longobardi B et al. Dosimetric and clinical predictors of toxicity following combined chemotherapy and moderately hypofractionated rotational radiotherapy of locally advanced pancreatic adenocarcinoma. *Radiother Oncol* 2013;108:66–71.
29. Crane CH. Hypofractionated ablative radiotherapy for locally advanced pancreatic cancer. *J Radiat Res* 2016;57:53–7.
30. Kelly P, Das P, Pinnix CC et al. Duodenal toxicity after fractionated chemoradiation for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2013;85:e143–9.