Clinical and Translational Radiation Oncology 31 (2021) 80–85

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Deterioration of pancreatic exocrine function in carbon ion radiotherapy for pancreatic cancer

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ARTICLE INFO

Keywords:
Carbon ion radiotherapy
Pancreatic cancer
Pancreatic function
Pancreatic exocrine insufficiency
Dose-volume histogram

ABSTRACT

Background and purpose: In radiotherapy (RT) for pancreatic cancer, the pancreas is considered an important organ at risk. However, there are insufficient reports on pancreatic function deterioration after X-ray RT as organ at risk, and there are no reports on those after carbon ion (C-ion) RT. Here, we evaluated pancreatic exocrine insufficiency (PEI) after C-ion RT using dose-volume histogram (DVH) analysis.

Materials and methods: Data were retrospectively collected from patients who had undergone C-ion RT for pancreatic cancer between July 2013 and June 2019. The prescribed C-ion doses were 55.2 Gy (relative biological effectiveness) in 12 fractions. Serum pancreatic amylase and lipase values were measured before and after C-ion RT. In DVH analysis, we assessed $V_{5Gy–50Gy}$ and $V_{<5Gy–50Gy}$ of pancreatic volume and analyzed whether these DVH parameters involved PEI.

Results: Thirty-three patients were included in the analysis. The median follow-up duration after the initiation of C-ion RT in these patients was 15.8 months (range, 4.3–64.8). During and after treatment, 57.6% of patients developed PEI within 13.6 months, defined as pancreatic amylase and lipase deficiencies. In DVH analysis, $V_{<5Gy}$ was the most effective factor for the PEI, and the cutoff value for developing PEI in $V_{<5Gy}$ was 4.57 cm^3.

Conclusion: We showed that pancreatic exocrine function declined after C-ion RT for pancreatic cancer and that PEI was initiated early in the course of C-ion RT. Additionally, a low dose of DVH parameters, such as $V_{<5Gy}$, was a prognostic factor of PEI.

1. Introduction

Pancreatic cancer is one of the most aggressive malignancies. Although surgical resection is the first-line radical treatment for pancreatic cancer, only 20% of pancreatic cancer patients are eligible for surgical treatment at diagnosis, and another 30% have locally advanced pancreatic tumors with nonmetastatic disease [1]. Chemotherapy alone or X-ray radiotherapy (RT) plus chemotherapy is a standard treatment option for locally advanced pancreatic cancer patients. However, the prognosis is extremely poor (median survival duration, 8.6–15.2 months) [2–5].

Carbon ion (C-ion) RT is a promising RT modality that presents higher dose localization and relative biological effectiveness (RBE) than X-ray RT [6]. Previous studies have shown that C-ion RT was a safe and effective treatment for various malignancies [7–11]. For inoperable locally advanced pancreatic cancer, C-ion RT is superior to X-ray RT, as previous studies have shown that 2-year overall survival (OS) and local control (LC) rates were approximately 46% and 70%, respectively, with tolerable gastrointestinal and hematological toxicities [7–9]. Although clinical outcomes such as OS, LC, and gastrointestinal toxicities have been analyzed in previous reports, the effect of C-ion RT on pancreatic function remains to be investigated.

The pancreas is one of the organs at risk of pancreatic cancer. Previous studies on abdominal X-ray RT have reported deterioration in pancreatic endocrine and exocrine function, and these results showed that the pancreas is a highly radiosensitive organ [12–19]. Suppose pancreatic cancer treatment causes pancreatic exocrine insufficiency (PEI), it might lead to dyspepsia, poor nutrition, diarrhea, and sarcopenia, affecting a patient's quality of life, additional treatment options for recurrence, and prognosis. However, there are insufficient reports of PEI caused by RT for pancreatic cancer, and there are no reports on C-ion RT. Hence, we evaluated the changes in pancreatic exocrine function in

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https://doi.org/10.1016/j.ctro.2021.09.007
Received 14 June 2021; Received in revised form 10 September 2021; Accepted 28 September 2021
Available online 3 October 2021

pancreatic cancer patients who underwent C-ion RT and the correlation of dosimetric factors with PEI development after C-ion RT.

2. Materials and methods

2.1. Patients

This retrospective study reviewed patients' medical records treated with C-ion RT for pancreatic cancer at Gunma University Heavy Ion Medical Center (GHMC) between July 2013 and June 2019. Patients were diagnosed according to histology or radiological imaging with computed tomography (CT) or magnetic resonance imaging. The inclusion criteria of this study were as follows: (1) patients with inoperable pancreatic cancer (with locally advanced stage, comorbidity, or refusal to undergo surgery as the reasons for inoperability), (2) patients with no distant metastasis, (3) patients with serum pancreatic amylase and lipase values before C-ion RT at normal levels, and (4) patients with performance status 0–2 according to the Eastern Cooperative Oncology Group classification. Individual informed consent was waived by the Gunma University institutional review board, and the study was approved with an opt-out of notification regarding this analysis before this study. All patients signed an informed consent form before the initiation of therapy.

2.2. Carbon ion radiotherapy and delineation of the normal pancreas

The dose of C-ion RT was calculated using XiO-N (version 4.47; Elekta AB, Stockholm, Sweden and Mitsubishi Electric, Tokyo, Japan) [6]. The radiation dose calculation for the target volume and the surrounding normal structures was expressed in Gy (RBE), which is defined as the physical dose multiplied by the RBE of C-ions [6]. Before C-ion RT, patients were immobilized using tailor-made fixation cushions and thermoplastic shells to acquire treatment planning CT images; respiratory-gated and four-dimensional CT images were acquired. In actual treatment, the gating level for respiratory-gated irradiation was within 30% of the wave height around the peak exhalation. Patients received C-ion RT once daily, 4 days a week (Tuesday to Friday).

Contrast-enhanced CT images were merged with treatment planning CT images to precisely delineate the gross tumor volume (GTV) and normal pancreas. The pancreas outside the GTV was defined as the normal pancreas. The clinical target volume (CTV) was defined as the GTV, including at least 5-mm margins in all directions. Prophylactic lymph nodes and neuroplexus regions were included in the CTV. The planning organ-at-risk volume (PRV) was obtained by adding a 2-mm margin to the gastrointestinal tract. Areas that overlapped with the PRV of the gastrointestinal tract were excluded from the CTV. The planning target volume (PTV) included the CTV with a 3-mm margin for possible positioning errors. When the PTV overlapped with an organ at risk, the margin was reduced accordingly.

The prescribed doses were 55.2 Gy (RBE) in 12 fractions for all patients. The dose constraints were as follows: for the stomach and duodenum, the maximum dose (D_{max}) < 45 Gy (RBE), the dose to 2 cm^3 [D_{2cc}] < 40 Gy (RBE), and volumes that received at least 30 Gy (RBE) (V_{30Gy}) < 10 cc; to the spinal cord, D_{max} < 30 Gy (RBE); to the CTV, CTV that received at least 95% of the prescribed dose (CTV $V_{95\%}$) > 99%.

2.3. Evaluation of pancreatic exocrine function

Serum pancreatic amylase and lipase values were measured before and after C-ion RT. The reference ranges for serum pancreatic amylase and lipase were 16.0–52.0 U/L and 13.0–55.0 U/L, respectively. PEI was defined when both serum pancreatic amylase and lipase values remained below the reference range after C-ion RT initiation. The values of serum pancreatic amylase and lipase at the following day after C-ion RT initiation were categorized as follows: day − 30 to − 8, "before"; day − 7 to 0, "start"; day 4 to 10, "1 week"; day 16 to 44, "1 month"; day 76 to 104, "3 months"; and day 335 to 395, "1 year." Acute and late toxicities of pancreatitis were evaluated as the highest grade of toxicity that occurred within 3 months and after 3 months after initiating C-ion RT, respectively. Pancreatitis was graded according to the Common Terminology Criteria for Adverse Events (version 4.0) of the National Cancer Institute [20].

2.4. Dose-volume histogram analysis

Dose-volume histogram (DVH) analysis was performed to evaluate the correlation between PEI and C-ion RT dose to the normal pancreas. We assessed the percentage of the normal pancreatic volume (i.e., the pancreas outside the GTV) that received at least 5, 10, 20, 30, 40, and 50 Gy (RBE) (V_{5Gy}, V_{10Gy}, V_{20Gy}, V_{30Gy}, V_{40Gy}, and V_{50Gy}) and the pancreatic volume that received<5, 10, 20, 30, 40, and 50 Gy (RBE) of the pancreas volume ($V_{<5Gy}$, $V_{<10Gy}$, $V_{<20Gy}$, $V_{<30Gy}$, $V_{<40Gy}$, and $V_{<50Gy}$) based on the DVH.

2.5. Statistical analyses

All statistical analyses were performed using the Statistical Package of the Social Sciences software version 25.0 (IBM Inc., Armonk, NY, USA) or R version 3.6.2 (R Core Team, Vienna, Austria). Fisher's exact test was used to test correlations between PEI and clinical factors such as age (≤72 or >72), sex (male or female), performance status (PS) (0 or 1, 2), chemotherapy (presence or absence), and tumor location (head or body, tail). The Wilcoxon signed-rank test was used to compare patient characteristics, serum amylase and lipase values, and DVH parameters ($V_{5Gy–50Gy}$ and $V_{<5Gy–50Gy}$) of the pancreas stratified by pancreatic exocrine status. We created a receiver operating characteristic (ROC) curve to determine the optimal cutoff values to develop the PEI in the DVH parameters. The cutoff value was defined according to the nearest point from the coordinates (0, 1) on the ROC graph. OS was measured from the date of initiation of C-ion RT to the date of death or most recent follow-up. Local control was defined as no evidence of local progression with no regrowth in tumor size on CT and no increase in fluorodeoxyglucose uptake on positron emitter tomography. The probabilities of OS and LC were calculated using the Kaplan-Meier method. We evaluated whether the absence or presence of PEI in OS and LC could be prognostic factors using the log-rank test. P-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Between July 2013 and June 2019, 180 patients with pancreatic cancer underwent C-ion RT in the GHMC. Of these, 33 patients whose serum pancreatic amylase and lipase values were within the reference ranges before C-ion RT were analyzed. Patients' clinical characteristics are summarized in Table 1. The median follow-up duration after the initiation of C-ion RT was 15.8 months (range, 4.3–64.8). Fig. 1 shows CT and 2-deoxy-2-[18F]fluoro-D-glucose (FDG)-positron emission tomography/CT images before C-ion RT and the dose distribution of a representative case.

3.2. Exocrine pancreatic function

The kinetics of serum pancreatic amylase and lipase values are shown in Fig. 2. There were significant differences in serum pancreatic amylase values between C-ion RT initiation and 1 month, 3 months, and 1 year after C-ion RT (P < 0.01, <0.01, and < 0.01, respectively) (Fig. 2C) and in lipase values at the start of C-ion RT and 1 week, 1 month, 3 months, and 1 year after C-ion RT (P < 0.01, <0.01, <0.01, and < 0.01, respectively) (Fig. 2D). One patient developed grade 2 pancreatitis with hyperlipasemia alone as acute toxicity. No patient

Table 1
Patient characteristics.

Characteristics	All (N = 33)	Absence of PEI (N = 14)	Presence of PEI (N = 19)	*P* value
Age, years, median (range)	72 (47–97)	72 (58–97)	74 (47–86)	0.19
Sex, number (%)				
Male	18 (54.5%)	8 (57.1%)	10 (52.6%)	0.80
Female	15 (45.5%)	6 (42.9%)	9 (47.4%)	
Performance status (%)				
0	10 (30.3%)	5 (35.7%)	5 (26.3%)	0.56
1, 2	23 (69.7%)	9 (64.3%)	14 (73.7%)	
Chemotherapy				
Presence	27 (81.8%)	10 (71.4%)	17 (89.5%)	0.23
Absence	6 (18.2%)	4 (28.6%)	2 (10.5%)	
Tumor location				
Head	14 (42.4%)	6 (42.9%)	8 (42.1%)	0.97
Body-tail	19 (57.6%)	8 (57.1%)	11 (57.9%)	
Serum pancreatic amylase before C-ion RT, U/L, median (range)	32.0 (16.0–51.0)	38.0 (20.0–51.0)	27.0 (16.0–50.0)	0.09
Serum lipase value before C-ion RT, U/L, median (range)	20.9 (14.0–44.4)	22.8 (15.6–43.6)	20.3 (14.0–44.4)	0.19

Abbreviations: PEI, pancreatic exocrine insufficiency.

developed pancreatitis due to late toxicity. During and after C-ion RT, 60.6% (20/33) of patients developed pancreatic amylase deficiency; they developed hypoamylasemia within 10.7 months. Moreover, 81.8% (27/33) of patients developed lipase deficiency; they developed hypolipasemia within 13.6 months, and 57.6% (19/33) of patients developed both deficiencies and PEI defined as both pancreatic amylase and lipase deficiencies within 13.6 months.

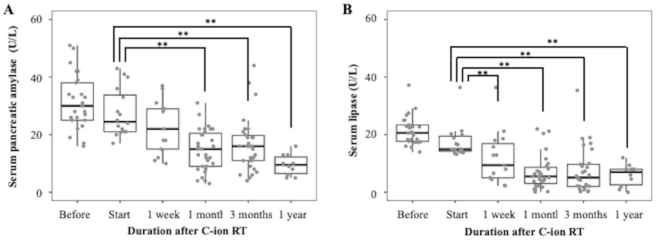

Fig. 2. Kinetics of serum pancreatic amylase and lipase values in all patients. (A) Box plots with the kinetics of serum pancreatic amylase values. (B) Box plots with the kinetics of serum lipase values. Significantly different at $^{**}P < 0.01$.

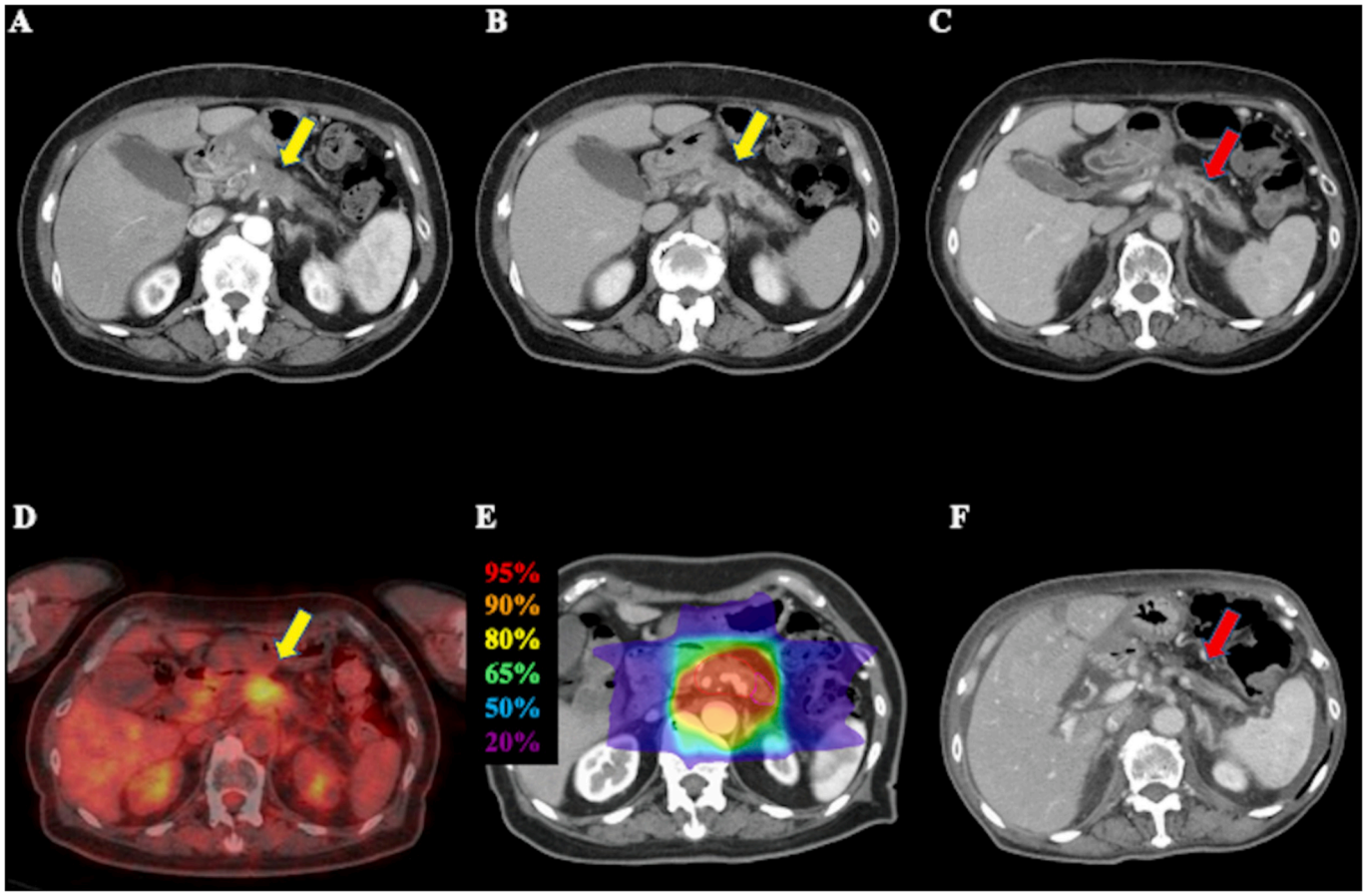

Fig. 1. The radiological images before and after carbon-ion radiotherapy (C-ion RT) and dose distribution of a 58-year-old woman with pancreatic body cancer. (A) Contrast-enhanced computed tomography (CT) of early phase before C-ion RT. The yellow arrow shows the tumor. (B) Contrast-enhanced CT of portal phase before C-ion RT. The yellow arrow shows the tumor. (C) Contours on axial CT images. The red arrow shows the pancreas. (D) 2-deoxy-2-[18F]fluoro-D-glucose (FDG)-positron emission tomography/CT. The yellow arrow shows the tumor with abnormal FDG uptake. (E) Dose distribution on axial CT images. The area within the red outline is GTV, and the magenta outline is the normal pancreas. Highlighted are the 95% (red), 90% (orange), 80% (yellow), 65% (green), 50% (blue), and 20% (purple) isodose curves (100% was 55.2 Gy [RBE]). (F) Contrast-enhanced CT of portal phase 1 year after C-ion RT. The red arrow shows the atrophy of the pancreas. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Correlations between clinical and dosimetric factors and pancreatic exocrine insufficiency

There was no significant difference in the probability of PEI between age (≤72 or >72), sex (male or female), PS (0 or 1, 2), chemotherapy (presence or absence), and tumor location (head or body, tail) (Table 1). Correlations of the DVH parameters with PEI are shown in Table 2. $V_{<5Gy}$, $V_{<10Gy}$, $V_{<20Gy}$, and $V_{<30Gy}$ were significantly lower in PEI patients. Cutoff values were determined using ROC curves. $V_{<5Gy}$, $V_{<10Gy}$, $V_{<20Gy}$, and $V_{<30Gy}$ smaller than 4.57 cm^3, 6.15 cm^3, 15.5 cm^3, and 16.3 cm^3, respectively, possibly affected PEI development (Fig. 3 and Table 3). In the ROC curve analysis, $V_{<5Gy}$ had the largest area under the curve for $V_{<5Gy}$, $V_{<10Gy}$, $V_{<20Gy}$, and $V_{<30Gy}$. Sixteen of 21 patients with $V_{<5Gy}$ smaller than 4.57 cm^3 developed PEI. The 1/2-year OS and LC rates in all patients were 75.3%/29.7% and 95.4%/70.9%, respectively. In the absence and presence of PEI analysis, the 1/2-year OS in the absence and presence of the PEI group were 78.6%/35.9% and 73.7%/25.3% ($P = 0.754$), respectively, and the 1/2-year LC rates in the absence and presence of the PEI group were 100%/80.0% and 93.3%/62.2% ($P = 0.591$), respectively. There were no significant differences between the presence or absence of PEI in OS and LC.

4. Discussion

This is the first study to examine the exacerbations of PEI caused by C-ion RT for pancreatic cancer. Serum pancreatic amylase and lipase levels significantly decreased early in the course of C-ion RT. Dosimetric analyses found that $V_{<5Gy}$, $V_{<10Gy}$, $V_{<20Gy}$, and $V_{<30Gy}$ of the pancreas were significantly lower in patients with pancreatic exocrine decline after C-ion RT. These findings provide novel evidence that is helpful in the management of C-ion RT for pancreatic cancer.

Evidence of PEI caused by RT for pancreatic cancer is extremely limited. Horst et al. have reported a decrease in amino acid consumption and fecal elastase-1 after chemoradiotherapy [12]. Yamaguchi et al. have shown that intraoperative irradiation increased the decline in exocrine function after pancreatic head resection [13]. Similar changes were reported in abdominal X-ray RT for other malignancies, such as gastric cancer [14,15]. This study is the first to show that a decline in pancreatic exocrine function also occurs in C-ion RT for pancreatic cancer.

The difference in the probability of PEI between C-ion RT and X-ray RT is of interest. Horst et al. have reported that 61.5% (8/13) of the patients developed a decrease in amino acid consumption, and 77.8% (7/9) had a decline in fecal elastase-1 after X-ray RT for pancreatic cancer [12]. Our findings that 60.6% (20/33) and 81.8% (27/33) of patients experienced hypoamylasemia and hypolipasemia, respectively, were similar to the results of their study. However, Wydmanski et al. have reported a lower incidence of hypoamylasemia (20%) and hypolipasemia (48%) after pre-or post-operative X-ray RT for gastric cancer [14]. This might be caused by differences in the irradiated volume of the pancreas since pre-or post-operative RT for gastric cancer had different treatment targets from definitive RT for pancreatic cancer. However, as their study had no DVH data for the pancreas, we could not verify this issue. Therefore, further studies are warranted.

In this study, the effect of C-ion RT on pancreatic exocrine function was accurately evaluated by eliminating patients with pancreatitis or pancreatic insufficiency before C-ion RT. The serum pancreatic amylase and lipase levels decreased from the early stage of treatment, with a significant difference from the value of "start" of C-ion RT and after the initiation of C-ion RT (e.g., "1 week," "1 month," "3 months," and "1 year"). This finding suggests that the pancreas may be a highly radiosensitive organ prone to PEI. In contrast, it is difficult to predict PEI from the pre-treatment serum pancreatic amylase and lipase values because even those with high pre-treatment values developed PEI. Additionally, this study revealed that if PEI caused by C-ion RT occurred, it would be difficult to recover to the original state of pancreatic exocrine function. Even with high-dose localization of C-ion RT, a high dose and a certain volume of irradiation to the normal pancreas may be inevitable when sufficient margins are taken for the radical cure of pancreatic cancer. However, PEI, which might cause low-grade diarrhea and anorexia, could be treated with digestive enzyme replacement therapy. Therefore, in the treatment planning of C-ion RT for pancreatic cancer, priority is given to target coverage; that is, there is no need to narrow the margin or

Table 2
Dose-volume histogram parameter analysis of pancreatic exocrine insufficiency.

Factors	Median volume (range)		*P* value
	Absence of PEI (N = 14)	Presence of PEI (N = 19)	
V_{5Gy} (cm^3)	39.16 (11.16–96.09)	33.67 (14.36–82.52)	0.51
V_{10Gy} (cm^3)	37.55 (10.57–94.78)	33.30 (12.86–77.64)	0.51
V_{20Gy} (cm^3)	23.61 (9.81–72.87)	27.10 (8.04–70.25)	0.98
V_{30Gy} (cm^3)	19.19 (8.46–61.24)	22.59 (6.70–63.52)	0.88
V_{40Gy} (cm^3)	16.62 (7.05–49.36)	17.79 (5.26–56.81)	0.79
V_{50Gy} (cm^3)	9.87 (5.53–35.60)	9.99 (3.18–43.90)	0.83
$V_{<5Gy}$ (cm^3)	5.32 (0–22.95)	1.98 (0–11.61)	0.01*
$V_{<10Gy}$ (cm^3)	6.87 (0–24.49)	3.48 (0–18.66)	0.01*
$V_{<20Gy}$ (cm^3)	21.22 (5.62–42.19)	8.37 (0.54–34.96)	0.04*
$V_{<30Gy}$ (cm^3)	25.89 (6.43–50.15)	14.35 (2.35–43.03)	0.04*
$V_{<40Gy}$ (cm^3)	34.80 (8.07–56.07)	19.45 (6.47–53.16)	0.07
$V_{<50Gy}$ (cm^3)	41.77 (9.98–63.94)	24.61 (8.91–67.12)	0.10

Abbreviations: PEI, pancreatic exocrine insufficiency; V_{5Gy}–V_{50Gy}, the percentage of the pancreatic volume that received at least 5–50 Gy (RBE); $V_{<5Gy}$–$V_{<50Gy}$, pancreatic volume that received<5–50 Gy (RBE). *$P < 0.05$

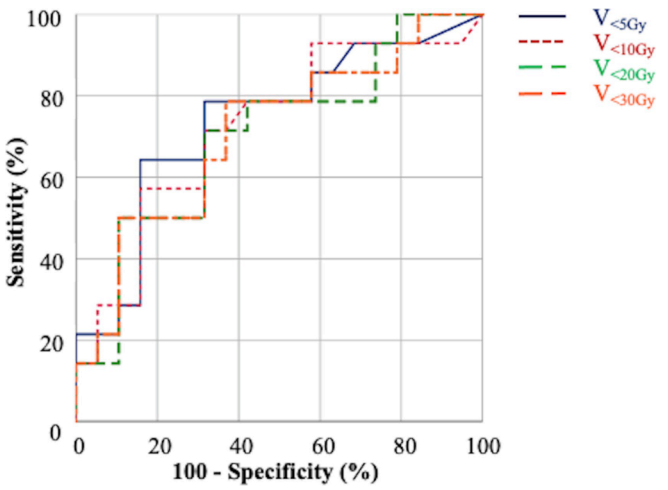

Fig. 3. Receiver operating characteristic curves for developing the pancreatic exocrine insufficiency in $V_{<5Gy}$, $V_{<10Gy}$, $V_{<20Gy}$, and $V_{<30Gy}$ of normal pancreas volume. The optimal cutoff values for developing the pancreatic exocrine insufficiency in $V_{<5Gy}$, $V_{<10Gy}$, $V_{<20Gy}$, and $V_{<30Gy}$ were 4.57 cm^3 (sensitivity, 78.6%; specificity, 68.4%), 6.15 cm^3 (sensitivity, 57.1%; specificity, 84.2%), 15.5 cm^3 (sensitivity, 71.4%; specificity, 68.4%), and 16.3 cm^3 (sensitivity, 78.6%; specificity, 63.2%), respectively.

Table 3
Results of the receiver operating characteristic curve analysis for factors of pancreatic exocrine insufficiency.

Factors	Median volume (range) (cm^3)	Cutoff value (cm^3)	Sensitivity, specificity	AUC	*P* value
$V_{<5Gy}$	3.45 (0–22.95)	4.57	78.6%, 68.4%	0.74	0.02*
$V_{<10Gy}$	4.61 (0–24.49)	6.15	57.1%, 84.2%	0.72	0.03*
$V_{<20Gy}$	15.43 (0.54–42.19)	15.5	71.4%, 68.4%	0.70	0.04*
$V_{<30Gy}$	17.79 (2.35–50.15)	16.3	78.6%, 63.2%	0.71	0.04*

Abbreviations: AUC, area under the receiver operating characteristic curve; $V_{<5Gy}$–$V_{<30Gy}$, pancreatic volume that received<5–30 Gy (RBE). *$P < 0.05$

reduce the prescribed dose to avoid PEI.

The DVH parameters were tested from the viewpoint of association with PEI (Table 3). There was no significant difference in V_{5Gy}, V_{10Gy}, V_{20Gy}, V_{30Gy}, and V_{40Gy} of the pancreas between patients with or without PEI. In contrast, $V_{<5Gy}$, $V_{<10Gy}$, $V_{<20Gy}$, and $V_{<30Gy}$ of the pancreas were significantly lower in patients who experienced PEI than in patients who did not, and $V_{<5Gy}$ would be the most effective factor because the area under the ROC curve is larger than other factors. $V_{<XGy}$ indicates the volume of the residual pancreas, and $V_{<XGy}$ might be superior to V_{XGy} as an indicator in DVH analysis of pancreatic function in C-ion RT because C-ion RT has a sharp dose fall-off and the less low-dose area around the target because of its higher dose localization property than X-ray RT [21]. Furthermore, we found significant deterioration in serum pancreatic amylase and lipase levels within 1 month (Fig. 2C, D). Accordingly, if the DVH parameters mentioned above expect PEI, early initiation of digestive enzyme replacement therapy could prevent digestive symptoms such as diarrhea and anorexia, which may cause body weight loss.

Maintaining the accuracy of treatment positioning is important for RT [22]. Although C-ion RT has a higher dose localization property than X-ray RT, the dose distribution of C-ion RT is highly positioning-sensitive because of the sharp dose gradient [22]. Theoretically, changes in the beam pathway due to body weight loss may cause dose distribution degradation because of the changing range of C-ion beams owing to changes in subcutaneous fat and visceral fat of the beam pathway. Therefore, the prevention of body weight loss during C-ion RT could improve the robustness of the C-ion RT. Previous studies have demonstrated that digestive enzyme replacement therapy for enzyme insufficiencies could reduce body weight loss [23–25]. Additionally, although PEI was not a prognostic factor for OS in this study, PEI has been reported as one of the prognostic factors for OS in pancreatic cancer [25]. Therefore, administration of pancreatic digestive enzymes during C-ion RT for pancreatic cancer could maintain treatment positioning accuracy. Furthermore, administration of pancreatic digestive enzymes might contribute to prolonged OS.

Pancreatic endocrine function after RT is also a concern. Several studies have shown endocrine failure after X-ray RT [15–18]; thus, those after C-ion RT also need to be examined. However, we could not evaluate insulin secretion because insulin secretion ability (blood and urinary C-peptide) was not usually measured in our clinical practice. Therefore, further studies are warranted.

This study had some limitations. First, this was a retrospective study with a relatively small population, which is a potential source of bias. Second, to simplify the interpretation of our results, patients with abnormal pancreatic exocrine function before C-ion RT were excluded from the analyses. C-ion RT for these patients should be examined in future studies. Third, the effects of chemotherapy and the pancreatic tumor itself on exocrine function have not been sufficiently evaluated. Although our analysis found that the use of chemotherapy was not associated with PEI, our study included various chemotherapy regimens (e.g., gemcitabine alone, S-1 alone, gemcitabine plus albumin-bound paclitaxel, combination of oxaliplatin, irinotecan, fluorouracil, and leucovorin) and timing of combination with C-ion RT (e.g., before, concurrent, and after C-ion RT). Moreover, the pancreatic tumor itself might be a risk factor for PEI. These factors of various chemotherapy regimens, the timing of combination therapy, and the pancreatic tumor itself may affect our results. Third, we have defined PEI as both pancreatic amylase and lipase deficiencies. However, there is a limited number of reports using pancreatic amylase and lipase in defining PEI [14]. Recently, the ^{13}C-mixed triglyceride breath test (^{13}C-MTBT) has been reported as one of the best clinical examination data to define PEI [26]; however, ^{13}C-MTBT was not usually measured in our clinical practice. In the future, we will consider including the examination of ^{13}C-MTBT before and after C-ion RT in PEI analysis.

5. Conclusion

Pancreatic exocrine function declines after C-ion RT for pancreatic cancer, and that PEI is initiated early in the course of C-ion RT. These results suggest that the pancreas is sensitive to C-ion beams. Additionally, in the prognostic factor analysis of PEI, $V_{<5Gy}$ was the most effective factor. The cutoff value of $V_{<5Gy}$ was 4.57 cm^3, and C-ion irradiation was administered over this cutoff level, with a high possibility of PEI.

Funding

This study received no external funding.

Data availability statement

The datasets generated for this study are available upon request to the corresponding author.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank all the patients involved in this study, our colleagues at Gunma University Heavy Ion Medical Center and Department of Radiation Oncology Gunma University Graduate School of Medicine, and Editage (www.editage.com) for English language editing.

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