Advances in Radiation Oncology (2020) **5**, 377-387

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

How Much Was the Elective Lymph Node Region Covered in Involved-Field Radiation Therapy for Locally Advanced Pancreatic Cancer? Evaluation of Overlap Between Gross Target Volume and Celiac Artery—Superior Mesenteric Artery Lymph Node Regions

Rei Umezawa, MD, PhD,[a,b,*] Yoshinori Ito, MD, PhD,[a,c] Akihisa Wakita, MSc,[a] Satoshi Nakamura, MSc,[a] Hiroyuki Okamoto, PhD,[a] Kana Takahashi, MD, PhD,[a] Koji Inaba, MD, PhD,[a] Naoya Murakami, MD, PhD,[a] Hiroshi Igaki, MD, PhD,[a] Keiichi Jingu, MD, PhD,[b] and Jun Itami, MD, PhD[a]

[a]Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan; [b]Department of Radiation Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan; and [c]Department of Radiation Oncology, Showa University School of Medicine, Tokyo, Japan

Received 20 May 2019; revised 24 August 2019; accepted 27 August 2019

Abstract

Purpose: The purpose of this study was to investigate the overlaps between gross target volume (GTV) and the celiac artery (CA) and superior mesenteric artery (SMA) lymph node regions and to examine the dose incidentally irradiated to the CA and SMA lymph node regions by involved-field radiation therapy (IFRT) for locally advanced pancreatic cancer (LAPC).

Methods and Materials: Fifty-nine patients who had LAPC without distant metastasis were included. They received IFRT at 50.4 Gy in 28 fractions with 3-dimensional conformal radiation therapy. We calculated the percentages of overlap of GTV in the CA and SMA lymph node regions and examined what cases tend to have an overlap. We also investigated the dose metrics of CA and SMA lymph node regions by IFRT and the frequency of CA or SMA lymph node metastasis after IFRT.

Results: The median GTV volume was 52.2 mL. Median overlap percentages in the CA and SMA lymph node regions were 39.2% and 28.6%, respectively. There was a significant correlation between GTV volume and SMA overlap percentage ($P < .001$). Although the SMA overlap percentage was higher in the pancreas head ($P = .028$), the CA overlap percentage was higher in the pancreas body or tail ($P = .002$). Median mean dose, D95, and minimum dose in the CA lymph node region were 50.1 Gy, 48.7 Gy, and 45.9 Gy, respectively, and those in the SMA lymph node region 49.9 Gy, 47.3 Gy, and 39.2 Gy, respectively. CA lymph node metastases after IFRT were detected in 4 patients (6.8%).

Sources of support: This work had no specific funding.

Disclosures: The authors have no conflicts of interest to disclose.

* Corresponding author: Rei Umezawa, MD, PhD; E-mail: reirei513@hotmail.com

https://doi.org/10.1016/j.adro.2019.08.014

Conclusions: An overlap between GTV and CA-SMA lymph node regions was detected in many patients, and the CA and SMA lymph node regions were irradiated incidentally even by IFRT. Prophylactic lymph node regions might not be necessary in radiation therapy planning of LAPC.

Introduction

Pancreatic cancer is one of the cancers with an extremely poor prognosis. Although surgery has been the only curative treatment, the number of patients who are eligible for surgery, even those with localized disease, is limited.[1] Overall survival in patients who do not undergo pancreatectomy is poor compared with that in patients who undergo pancreatectomy for locally advanced pancreatic cancer (LAPC).[2]

Chemoradiotherapy is one of the treatment options for patients with unresectable LAPC. Regional lymph node metastasis is often detected in patients with LAPC,[3-5] and it is an important prognostic factor.[6,7] Therefore, we need to consider including elective lymph nodes in the clinical target volume (CTV) in radiation therapy (RT) planning for LAPC. However, the irradiated volume was shown to be significantly correlated with the development of acute intestinal toxicity.[8] Although some guidelines recommend that the elective lymph node region should be included in the CTV,[9,10] there have been some studies in which involved-field radiation therapy (IFRT) was used for LAPC.[11-13] Thus, it remains unclear whether elective lymph nodes should be included in the CTV in RT planning for LAPC.

In pancreatic cancer, the celiac artery (CA) and superior mesenteric artery (SMA) are very important blood vessels to decide the indication for surgery. Some studies have shown that most recurrences were in regions around the CA and SMA,[14,15] and it is considered important in RT planning for LAPC to judge whether to include the CA and SMA lymph node regions. However, because the incidence of CA or SMA involvement in LAPC is high, the gross target volume (GTV) would include those lymph node regions in many patients. Therefore, we considered that the elective lymph node region would be covered to some extent even with IFRT, and we hypothesized that analysis of the degree of overlap between the GTV and CA-SMA region would be helpful for solving the controversy about prophylactic node regions in the CTV. We also considered that a part of the elective lymph node region would be irradiated incidentally in IFRT and that the frequency of lymph node metastasis after IFRT would be low. There are also some reports about incidental irradiation to elective lymph nodes by IFRT in patients with advanced non-small cell lung cancer.[16,17] Furthermore, pancreatic cancer is likely to show continuous spreading via neural routes,[18] and neural invasion is observed in the soft tissue adherent to vessels, such as the CA and SMA.[19-21] Neural invasion is a poor prognostic factor in addition to lymph node metastasis for LAPC,[7,22,23] and we hypothesized that the overlap in CA and SMA lymph node regions might be associated with treatment outcomes.

The primary purpose of this study was to investigate the overlaps between the GTV and the CA and SMA regions and to examine the dose incidentally irradiated to the CT and SMA regions by IFRT. The secondary purpose of this study was to determine the frequency of CA and SMA lymph node metastasis after IFRT and to determine whether that overlap is a prognostic factor in CRT for LAPC.

Methods

Patients

LAPC patients who underwent IFRT in our institution between January 2007 and March 2015 were analyzed. We selected patients with stage III cancer (T4N0-1M0; seventh edition of the TNM proposed by International Union Against Cancer) at the initial diagnosis. This study was approved by the institutional review board of National Cancer Center (2016-058).

Treatment

Concurrent chemoradiotherapy was performed as first-line or second- and third-line treatment in all patients. IFRT was delivered with a total dose of 50.4 Gy in 28 fractions. S-1 was administered orally at a dose of 80 mg/m^2 twice daily on the day of radiation therapy.

Radiation therapy planning

Three-dimensional conformal radiation therapy (3DCRT) was delivered in all patients. Treatment planning by CT was performed in all patients. Intravenous contrast medium was administered, and the slice thickness

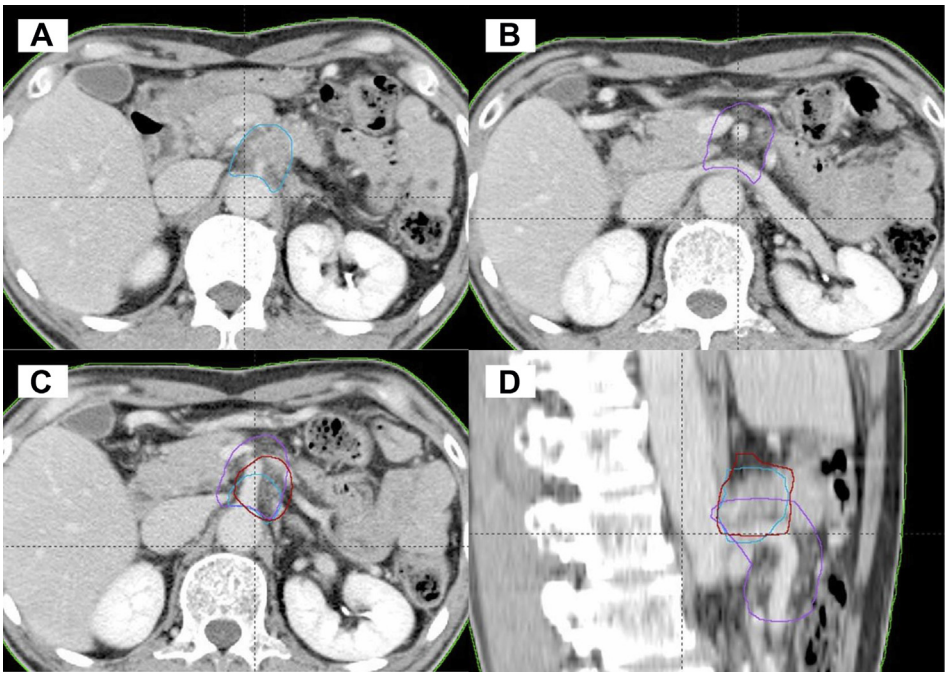

Figure 1 Example of contouring of the celiac artery lymph node region (A, blue line) and superior mesenteric artery lymph node region (B, purple line). We investigated the overlaps of the GTV (red line) in those lymph node regions (C and D).

of the CT scan was 2 mm. GTV was defined as the primary tumor and metastatic lymph nodes identified on CT. The CTV was defined as GTV plus 5 mm. Regional lymph nodes were not included electively. The planning target volume (PTV) was defined as CTV plus 10-mm margins except in the cranio-caudal directions, where 10- to 20-mm margins were added owing to the irradiation under free breathing. Contouring of the CA and SMA was based on reports by Goodman et al and Caravatta et al (Fig 1A and Fig 1B).[9,19] In CA contouring, the most proximal 1.0 to 1.5 cm from the root of the CA (to the first branching) was included. Then the CA was expanded by 1.0 cm in all directions. In SMA contouring, the most proximal 2.5 cm from the root of the SMA was included. Then the SMA was expanded by 1.0 cm in all directions.

$$Overlap\ percentage = \frac{Volume\ of\ GTV\ contained\ in\ the\ lymph\ node\ region}{Volume\ of\ the\ lymph\ node\ region}$$

This margin was not extended into other normal tissues or structures. Radiation therapy was delivered with photon beams of 15 or 20 MV using a linear accelerator. Four or 5 field techniques were used, 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 the analytical anisotropic algorithm.

Evaluation of CA and SMA lymph node metastasis after IFRT

We investigated the frequency of CA or SMA lymph node metastasis after IFRT. We defined a node of >10 mm in its minor axis as lymph node metastasis by a CT scan.

Statistical analysis

We examined the GTV and the volume of the CA and SMA lymph node regions and calculated the overlap percentages of GTV included in the CA and SMA lymph node regions (Fig 1C and Fig 1D). The overlap percentage was calculated by the following formula:

Then we investigated in what kind of cases the overlap tended to be detected as follows. We evaluated the relation between overlap percentage and GTV volume by Spearman's rank-correlation coefficient. We defined $|r_s| > 0.7$ as a strong correlation, $0.4 \leq |r_s| < 0.7$ as a moderate correlation and $|r_s| < 0.4$ as a weak correlation. Moreover, we examined the differences between the overlap percentages in the CA and SMA lymph node regions and

tumor locations (pancreas head and pancreas body or tail carcinoma) by the Mann-Whitney *U* test.

We investigated the dose metrics (mean dose, D95 [dose covering at least 95% of the volume] and minimum dose) of the CA and SMA lymph node regions. We investigated the relations between GTV and dose metrics in the CA and SMA lymph node regions by Spearman's rank-correlation coefficient, and we examined the differences in dose metrics in the CA and SMA lymph node regions between pancreas head carcinoma and pancreas body or tail carcinoma by the Mann-Whitney *U* test. Moreover, we examined the association between the overlap percentage or dose metrics and lymph node metastasis in the CA and SMA lymph node regions after CRT by the Mann-Whitney *U* test.

Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. PFS was measured from the start of CRT to the date of the first relapse or death owing to any cause. OS was measured from the start of CRT to the date of death. Patients lost to follow-up were censored at the time of the last follow-up observation in each survival. Survival curves were drawn by the Kaplan-Meier method. Differences of PFS and OS between patient subgroups for prognostic factors and dose metrics of the CA and SMA lymph node regions were analyzed using the log-rank test in univariable analysis. With regard to the factors in continuous variables, analyses were performed by dividing the 2 groups with reference to each mean or median value. Multivariable analysis was performed with prognostic factors with $P < .1$ in univariable analysis using a Cox proportional hazards regression model.

Statistical significance was set at the level of $P < .05$. Statistical analysis was performed using JMP@10 (SAS Institute Inc, Cary, NC).

Table 1 Characteristics of patients in each group (N = 59)

Characteristic	Median (%)
Age at radiation therapy, in years, median (IQR)	64 (58-69)
Sex	
Male	30 (51)
Female	29 (49)
Tumor location	
Head	33 (56)
Body or tail	26 (44)
Nodal status	
Positive	17 (29)
Negative	42 (71)
CA19-9, median (IQR)	383 U/mL (92-583 U/mL)
Performance status	
0	18 (31)
1	41 (69)
Chemotherapy before radiation therapy	
Yes	31 (53)
GEM	26
GEM + S-1	3
S-1	1
FOLFIRINOX	1
No	28 (47)
Maintenance chemotherapy after radiation therapy	
Yes	37 (63)
S-1	23
GEM	11
GEM + S-1	2
GEM + Erlotinib	1
No	22 (37)

Abbreviations: FOLFIRINOX = oxaliplatin, irinotecan, 5-FU, and leucovorin; GEM = gemcitabine; IQR = interquartile range.

Results

Patient characteristics

Fifty-nine LAPC patients without distant metastasis who received CRT were analyzed. Patient characteristics are shown in Table 1.

Results of evaluation of the overlaps of GTV in the CA and SMA lymph node regions

The median GTV volume was 52.2 mL (interquartile range [IQR], 25.9-77.6 mL). Median volumes of the CA and SMA lymph node regions were 19.5 mL (IQR, 15.9-21.6 mL) and 31.2 mL (IQR, 26.5-36.0 mL), respectively. Median overlap percentages in the CA and SMA lymph node regions were 39.2% (IQR, 5.4%-69.5%) and 28.6% (IQR, 17.5%-56.3%), respectively. There was a significant correlation between GTV and overlap percentage in the SMA lymph node region ($r_s = 0.439$, $P < .001$), but not between GTV and overlap percentage in the CA lymph node region ($r_s = 0.222$, $P = .09$; Fig 2A and B). On the other hand, there was a significant difference between overlap percentage and tumor location in the CA lymph node region ($P < .001$), but not between overlap percentage and tumor location in the SMA lymph node region ($P = .927$; Fig 2C and D). Median overlap percentages of the CA lymph node region in the pancreas body or tail and in the pancreas head were 61.0% (IQR, 37.9%-83.2%) and 13.2% (IQR, 0%-53.9%), respectively. Median overlap percentages of the SMA lymph node region in the pancreas body or tail and in the pancreas head were 34.1% (IQR, 18.0%-47.4%) and 26.1% (IQR, 13.9%-64.0%), respectively. Thus, although the SMA overlap percentage was higher than the CA overlap percentage in the pancreas head ($P =$

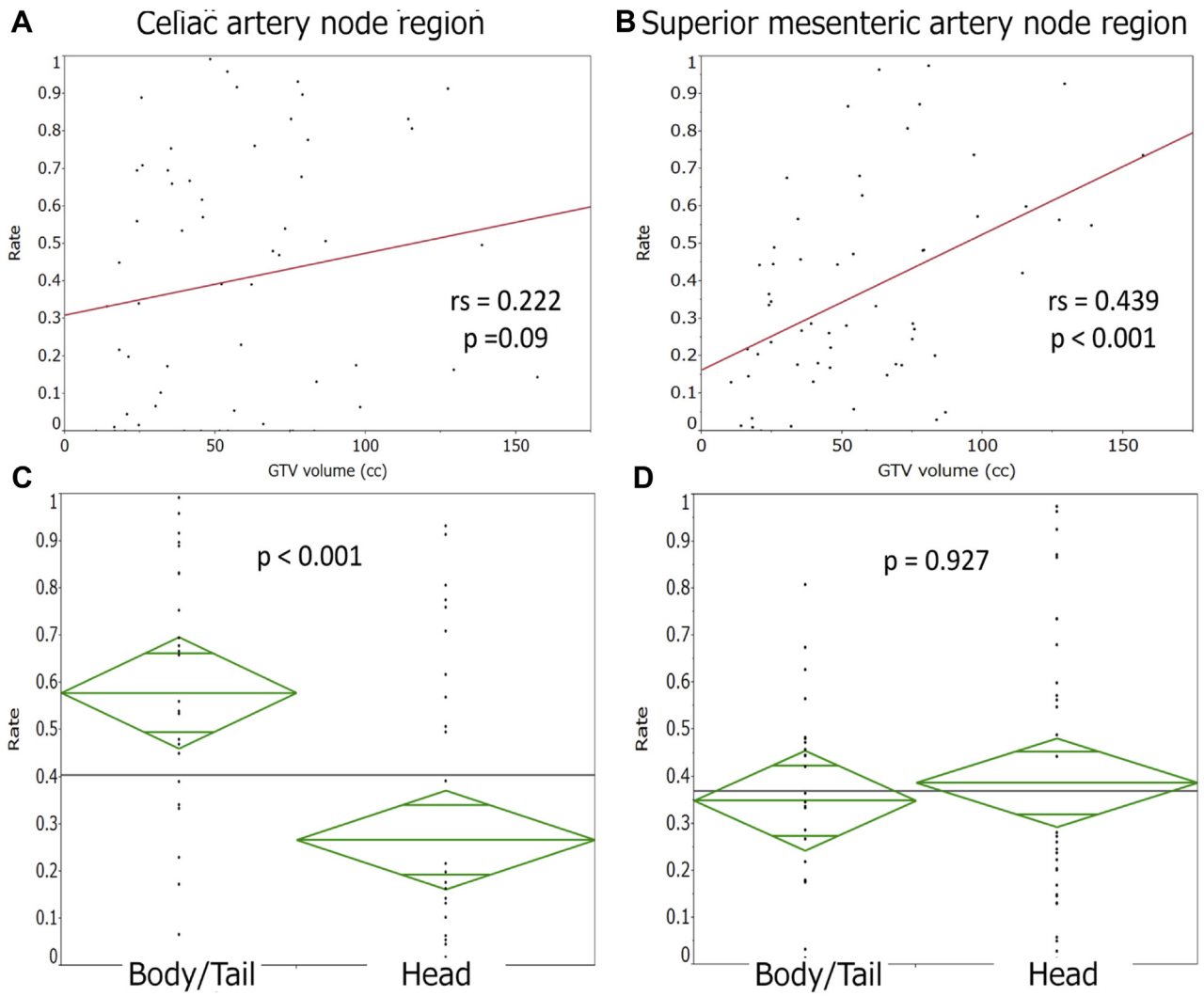

Figure 2 Correlations between gross target volume and overlap percentages in the celiac artery and superior mesenteric artery lymph node regions (A and B) and correlations between overlap percentages of the celiac artery and superior mesenteric artery lymph node regions in patients with carcinoma of the pancreas body or tail and patients with carcinoma of the pancreas head (C and D).

.028), the CA overlap percentage was higher than the SMA overlap percentage in the pancreas body or tail ($P = .002$).

Results of incidental irradiation to CA and SMA lymph nodes

Median mean dose, D95, and minimum dose in the CA and SMA lymph node regions were 50.1 Gy (IQR, 40.8-50.7 Gy) and 49.9 Gy (IQR, 48.0-50.7 Gy), 48.7 Gy (IQR, 12.2-50.0 Gy) and 47.3 Gy (IQR, 31.0-49.8 Gy), and 45.9 Gy (IQR, 6.2-49.7 Gy) and 39.2 Gy (IQR, 13.2-48.2 Gy), respectively. GTV volume was significantly correlated with mean dose and D95 in the SMA lymph node region ($r_s = 0.282$ and 0.263, $P = .03$ and .044) but not in the CA lymph node region ($r_s = 0.131$ and 0.07, $P = .325$ and .601; Fig 3A, B, E, and F). There were significant differences between mean dose, D95, minimum dose and tumor location in the CA lymph node region ($P < .001$, $< .001$, and $< .001$), but not in the SMA lymph node region ($P = .265$, .397, and 0.418; Fig 3C, D, G, H, K, and L). Median mean dose, D95, and minimum dose of the CA lymph node region in pancreas body or tail carcinoma were 50.5 Gy (IQR, 50.1-50.8 Gy), 50.0 Gy (IQR, 48.8-50.3 Gy), and 49.3 Gy (IQR, 45.8-50.0 Gy), respectively, and those in pancreas head carcinoma were 45.6 Gy (IQR, 36.1-50.3 Gy), 26.4 Gy (IQR, 7.2-48.9 Gy), and 23.9 Gy (IQR, 4.1-47.6 Gy), respectively. Median mean dose, D95, and minimum dose of the SMA lymph node region in pancreas body or tail carcinoma were 50.4 Gy (IQR, 47.7-50.8 Gy), 49.0 Gy (IQR, 25.9-50.1 Gy), and 44.0 Gy (IQR, 11.2-48.9 Gy), respectively, and those in pancreas head carcinoma were 49.6 Gy (IQR, 48.3-50.6 Gy), 46.5 Gy (IQR, 34.0-49.5 Gy), and 31.2 Gy (IQR, 20.6-47.9 Gy), respectively.

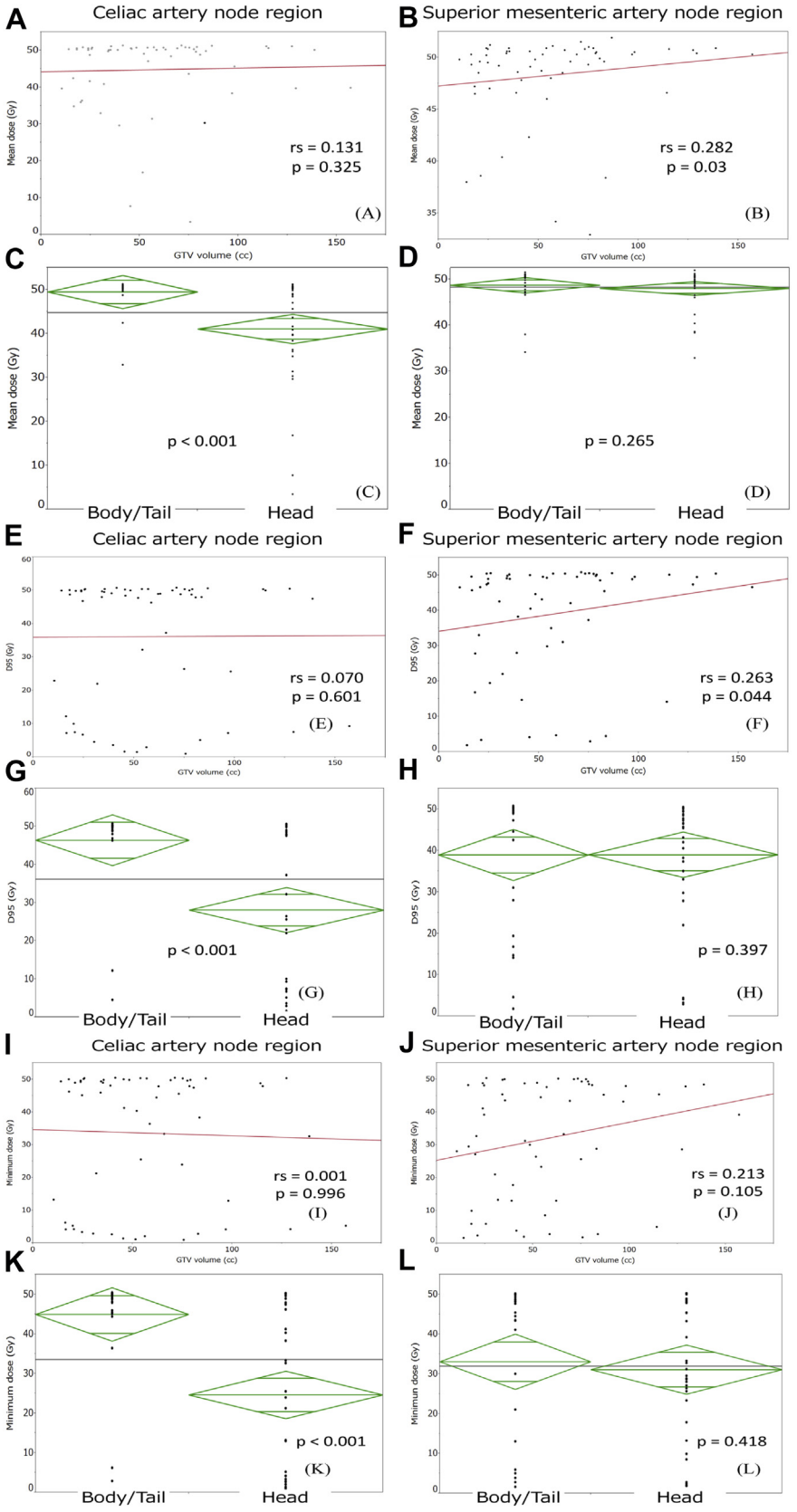

Figure 3 Correlations between gross target volume and mean dose (A and B), D95 (E and F), and minimum dose (I and J) in the celiac artery and superior mesenteric artery lymph node regions and correlations between mean dose (C and D), D95 (G and H), and minimum dose (K and L) in the celiac artery and superior mesenteric artery lymph node regions in patients with carcinoma of the pancreas body or tail and patients with carcinoma of the pancreas head.

Treatment outcomes

Although RT was discontinued at 46.8 Gy in 26 fractions in one patient, CRT was completed in the other patients. The median follow-up period from the start of IFRT was 14.4 months (range, 2.8-98.8 months). The 1-year OS and PFS rates were 62.1% (95% confidence interval [CI], 48.8%-73.9%) and 37.1% (95% CI, 25.7-50.3), respectively (Fig E1, available online at https://doi.org/10.1016/j.adro.2019.08.014). The patterns of first progression disease were distant metastases in 19 patients, local progression of the pancreatic tumor in 16 patients, and both in 15 patients. CA or SMA lymph node metastases after IFRT were detected in 4 patients. The details of the patients with lymph node metastasis are shown in Table 2. There were significant differences in the mean dose, D95, and minimum dose of CA lymph node regions between patients with and those without CA lymph node metastasis after CRT ($P = .048$, .039, and 0.040) but not in the overlap percentage ($P = .103$). Median CA mean dose, D95, and minimum dose in patients with CA lymph node metastasis after CRT were 39.8 Gy (IQR, 37.2-41.8 Gy), 8.4 Gy (IQR, 7.4-11.5 Gy) and 4.7 Gy (IQR, 4.2-6.0 Gy), respectively, and those in patients without CA lymph node metastasis were 50.1 Gy (IQR, 43.6-50.7 Gy), 48.8 Gy (IQR, 25.6-50.1 Gy), and 47.4 Gy (IQR, 21.2-49.8 Gy), respectively. Distant metastasis as first recurrence was detected in all patients in whom CA lymph node metastasis was detected after CRT.

Results of univariable and multivariable analyses of OS and PFS are shown in Table 3. GTV volume was a significant prognostic factor for both PFS and OS in univariable analysis, but not in multivariable analysis. However, there were no significant differences in PFS and OS in the CA and SMA overlaps. In univariable analysis, SMA mean dose and SMA D95 were significant prognostic factors in OS and SMA D95 was a significant prognostic factor in PFS.

Discussion

Recently, results of studies on intensity modulated radiation therapy (IMRT) for LAPC have been reported,[24-26] and reports about stereotactic radiation therapy (SRT) have been increasing.[27,28] Because pancreatic cancer has the feature of resistance to RT, the concept of administering a high dose of irradiation to a local region rather than including elective lymph nodes may be reasonable. It is expected that GTV would include a part of the elective lymph node regions and that there would be incidental irradiation to those regions even with IFRT. By examining this matter in detail, we consider that IFRT should be recommended more strongly for LAPC.

As expected, we found that GTV included in part of the CA and SMA lymph node regions in most of the patients. Moreover, we demonstrated that the overlap percentage of CA or SMA varies depending on the primary site. Past studies also showed that the frequency of lymph node metastasis varies depending on the tumor localization,[5,29] and the results of those past studies were similar to the overlap percentages in the present study. Although the frequency of CA lymph node metastasis tended to be higher in patients with carcinoma of the pancreatic body or tail, the frequency of SMA lymph node metastasis tended to be higher in patients with carcinoma of the pancreatic head. Deki et al reported that normal peripancreatic lymphatic networks are anatomically divided into 4 major pathways,[30] and consideration should be given to setting the range of a lymph node region based on those networks. However, we need to consider perineural invasion for understanding lymph node metastasis in LAPC. Kayahara et al suggested that neural invasion might be a pathway to lymphatic involvement.[31] Considering this, it may be better to focus on more intensive local irradiation to prevent lymph node metastasis. Moreover, OS and PFS were poor in patients with a large GTV in the present study, and some past studies showed that tumor size was a prognostic factor in

Table 2 Detail of patients with lymph node metastasis after RT

	LN metastasis	Out of field	Chemotherapy before and after CRT	Length from RT to LN metastasis	First recurrence	GTV volume	CA overlap percentage	CA Mean dose	CA D95	CA Minimum dose
Case 1	Celiac	Yes	GEM (before) S-1 (after)	25.5 mo	No (liver metastasis)	20.7 mL	4.50%	36.3 Gy	7.4 Gy	4.2 Gy
Case 2	Celiac	Yes	GEM (before) S-1 (after)	5.8 mo	No (liver metastasis)	156.2 mL	14.30%	39.8 Gy	9.3 Gy	5.2 Gy
Case 3	Celiac	Yes	GEM (before) S-1 (after)	5.1 mo	No (peritoneal dissemination)	129.3 mL	16.30%	39.7 Gy	7.5 Gy	4.2 Gy
Case 4	Celiac	Yes	None (before) GEM (after)	10.2 mo	No (liver metastasis)	16.4 mL	1%	42.4 Gy	12.2 Gy	6.2 Gy

Abbreviations: CA = celiac artery; GEM = gemcitabine; GTV = gross target volume; LN = lymph node; RT = radiation therapy; SMA = superior mesenteric artery.

Table 3 Results of univariable and multivariable analyses of overall survival and progression-free survival

Factor	Median OS time (mo)	UA		MA		Median PFS time (mo)	UA		MA	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age at radiation therapy			.29					.254		
<65 y	19.9	1				10.6	1			
≥65 y	14.4	1.36 (0.76-2.46)				7.7	1.38 (0.79-2.40)			
Sex			.935					.421		
Male	16.3	1				11.3	1			
Female	15.7	0.98 (0.55-1.74)				9.6	1.25 (0.72-2.17)			
Tumor location			.964					.979		
Head	17.9	1				9.9	1			
Body or tail	16.3	1.01 (0.56-1.81)				10	1.01 (0.58-1.74)			
Nodal status			.876					.604		
Positive	16.6	1				9.6	1			
Negative	14.8	1.05 (0.57-2.08)				10	0.85 (0.48-1.61)			
CA19-9			.086		0.209			.128		
≤400 U/mL	19.9	1		1		10.6	1			
>400 U/mL	14.1	1.65 (0.92-2.97)		1.53 (0.80-2.88)		7.7	1.52 (0.88-2.64)			
Performance status			.045		0.274			.078		.151
0	27.7	1		1		14.1	1		1	
1	14.1	1.92 (1.03-3.81)		1.50 (0.73-3.24)		9.6	1.70 (0.65-3.17)		1.56 (0.85-2.98)	
GTV volume			.016		0.178			.026		.077
≤60 mL	20.2	1		1		10.8	1		1	
>60 mL	9.4	2.00 (1.12-3.58)		1.52 (0.82-2.80)		5.5	1.85 (1.06-3.20)		1.51 (0.84-2.67)	
CA overlap percentage			.868					.939		
≤40%	17.9	1				9.9	1			
>40%	13.7	1.04 (0.59-1.87)				10	0.98 (0.56-1.69)			
SMA overlap perecntage			.772					.6		
≤40%	14.8	1				9.9	1			
>40%	19.9	0.92 (0.51-1.64)				10	0.86 (0.49-1.50)			
CA mean dose			.471					.234		
≤45 Gy	14.4	1				9.6	1			
>45 Gy	16.6	0.79 (0.43-1.53)				10.6	0.70 (0.39-1.30)			
SMA mean dose			.09		0.645			.145		
≤45 Gy	20.2	1		1		11.3	1			
>45 Gy	13.7	1.68 (0.93-3.16)		1.25 (0.51-3.76)		9.6	1.53 (0.87-2.77)			
CA D95			.576					.543		
≤40 Gy	17.9	1				9.9	1			
>40 Gy	16.3	0.84 (0.47-1.57)				10	0.84 (0.48-1.50)			

(*continued on next page*)

Table 3 (*continued*)

Factor	Median OS time (mo)	UA		MA		Median PFS time (mo)	UA		MA	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value		HR (95% CI)	*P* value	HR (95% CI)	*P* value
SMA D95			.043		0.439			.053		.103
≤40 Gy	21.7	1		1		12.3	1		1	
>40 Gy	13.7	2.01 (1.04-4.18)		1.56 (0.48-5.51)		9.7	1.85 (1.01-3.59)		1.70 (0.90-3.37)	
CA minimum dose			.483					.427		
≤30 Gy	14.8	1				9.8	1			
>30 Gy	16.3	0.80 (0.44-1.51)				10	0.79 (0.45-1.44)			
SMA minimum dose			.772					.212		
≤30 Gy	20.2	1				11.3	1			
>30 Gy	13.7	1.55 (0.87-2.88)				9.6	1.43 (0.82-2.54)			

Abbreviations: CA = celiac artery; HR = hazard ratio; MA = multivariable analysis; OS = overall survival; PFS = progression-free survival; UA = univariable analysis; SMA = superior mesenteric artery.

CRT and surgery for pancreatic cancer.[32-34] Those results indicate that it may be better to perform IFRT by dose escalation for LAPC with a large tumor size.

In the present study, there was incidental irradiation to the CA and SMA lymph node regions in most of the patients with LAPC. Fokas et al also analyzed the dosimetric coverage to lymph node regions in guidelines with inclusion of (Oxford and RTOG guidelines) and without inclusion of (Michigan and SCALOP guidelines) elective lymph node regions by 3DCRT (50.4 Gy in 28 fractions) in patients with LAPC.[35] The incidental mean irradiation doses by the SCALOP and Michigan guidelines to the SMA (approximately 35 Gy and 30 Gy, respectively) and CA (approximately 20 Gy and 25 Gy) were relatively high. However, CA lymph node metastasis after CRT was observed in 4 patients in the present study, although SMA lymph node metastasis was not detected. It is assumed that the PTV margin in IMRT and SRT would be small and that the dose irradiated to elective lymph nodes would be reduced compared with those in 3DCRT. Baine et al also reported that 15.9% of patients with LAPC who received SRT with a median dose of 35 Gy had regional recurrence out of the field and that all of the out-of-field failures occurred in areas that received <26 Gy.[36] However, distant metastasis as the first recurrence was detected in those patients in the present study, and it seems that this regional recurrence out of the field is acceptable. Furthermore, the frequency of the use of more intensive chemotherapy regimens such as FOLFIRINOX (oxaliplatin, irinotecan, 5-FU, and leucovorin) and nab-Paclitaxel plus gemcitabine (GEM) has been increasing, and those regimens have shown better treatment results than GEM alone.[37,38] Therefore, it might be possible to control micrometastases by using the combination of IFRT and higher intensity chemotherapies. This might lead to the concept that local irradiation can be used even if the tumor size is small.

In the present study, OS and PFS were good for patients in whom the dose to the SMA lymph node region was low. One of those reasons may be the degree of infiltration of the SMA. The neural plexuses around the SMA are most likely to be involved by perineural invasion.[39] There was also a significant correlation between GTV volume and overlap percentage in the SMA lymph node region in the present study. As mentioned earlier, neural invasion has been reported to be a poor prognostic factor.[7,22,23] However, no significant correlation was found between the overlap percentage in the CA or SMA lymph node region and treatment outcomes. A possible reason for those results is that neural invasion was evaluated solely by the degree to which the tumor was included in the CA or SMA region, not by pathologic findings.

There were some limitations in the present study. First, because our study was an evaluation of 3DCRT, our results would not necessarily be applicable to IMRT or SRT. Local failures was higher in our series (31 out of 59 patients) compared with other series using IMRT and SBRT and may have affected the emergence and detection of nodal failures. In addition, because 3DCRT was delivered using free breathing, wide PTV margins were used in these series, thereby increasing incidental dose.

Second, because of the retrospective analysis, there is a possibility that the contents of chemotherapy before irradiation and after irradiation differed considerably, which could affect treatment outcome. Moreover, there were few cases treated with FOLFIRINOX and nab-Paclitaxel plus GEM, which may also have affected regional lymph node recurrence. Third, it was difficult to identify the GTV at the time of RT planning for LAPC because MRI was not performed in some patients.

Conclusions

An overlap between GTV and CA-SMA lymph node regions was detected in many patients, and CA-SMA regions were irradiated incidentally even by IFRT. Because the frequency of lymph node metastases after CRT was low and GTV volume was shown to be a poor prognostic factor, contouring of prophylactic node regions might not be necessary in LAPC.

Acknowledgments

The authors thank all the patients who participated in the present study and all of the staff of the Department of Radiation Oncology in National Cancer Center Hospital for support of the present study.

Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2019.08.014.

References

1. Willett CG, Czito BG, Bendell JC, et al. Locally advanced pancreatic cancer. *J Clin Oncol*. 2005;23:4538-4544.
2. Katz MH, Pisters PW, Evans DB, et al. Borderline resectable pancreatic cancer: The importance of this emerging stage of disease. *J Am Coll Surg*. 2008;206:833-846; discussion 846-838.
3. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: Results, outcomes, and prognostic indicators. *J Gastrointest Surg*. 2000;4:567-579.
4. Shimada K, Sakamoto Y, Sano T, et al. Prognostic factors after distal pancreatectomy with extended lymphadenectomy for invasive pancreatic adenocarcinoma of the body and tail. *Surgery*. 2006;139:288-295.
5. Kayahara M, Nagakawa T, Ohta T, et al. Analysis of paraaortic lymph node involvement in pancreatic carcinoma: A significant indication for surgery? *Cancer*. 1999;85:583-590.
6. Asiyanbola B, Gleisner A, Herman JM, et al. Determining pattern of recurrence following pancreaticoduodenectomy and adjuvant 5-flurouracil-based chemoradiation therapy: Effect of number of metastatic lymph nodes and lymph node ratio. *J Gastrointest Surg*. 2009;13:752-759.
7. Takahashi H, Ohigashi H, Ishikawa O, et al. Perineural invasion and lymph node involvement as indicators of surgical outcome and pattern of recurrence in the setting of preoperative gemcitabine-based chemoradiation therapy for resectable pancreatic cancer. *Ann Surg*. 2012;255:95-102.
8. 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;26:3755-3759.
9. Goodman KA, Regine WF, Dawson LA, et al. Radiation Therapy Oncology Group consensus panel guidelines for the delineation of the clinical target volume in the postoperative treatment of pancreatic head cancer. *Int J Radiat Oncol Biol Phys*. 2012;83:901-908.
10. Brunner TB, Merkel S, Grabenbauer GG, et al. Definition of elective lymphatic target volume in ductal carcinoma of the pancreatic head based on histopathologic analysis. *Int J Radiat Oncol Biol Phys*. 2005;62:1021-1029.
11. Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2007;68:801-808.
12. 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;85:163-169.
13. 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;315:1844-1853.
14. Dholakia AS, Kumar R, Raman SP, et al. Mapping patterns of local recurrence after pancreaticoduodenectomy for pancreatic adenocarcinoma: A new approach to adjuvant radiation field design. *Int J Radiat Oncol Biol Phys*. 2013;87:1007-1015.
15. Heye T, Zausig N, Klauss M, et al. CT diagnosis of recurrence after pancreatic cancer: Is there a pattern? *World J Gastroenterol*. 2011;17:1126-1134.
16. Kimura T, Togami T, Nishiyama Y, et al. Impact of incidental irradiation on clinically uninvolved nodal regions in patients with advanced non-small-cell lung cancer treated with involved-field radiation therapy: Does incidental irradiation contribute to the low incidence of elective nodal failure? *Int J Radiat Oncol Biol Phys*. 2010;77:337-343.
17. Kepka L, Maciejewski B, Withers RH. Does incidental irradiation with doses below 50 gy effectively reduce isolated nodal failures in non-small-cell lung cancer: Dose-response relationship. *Int J Radiat Oncol Biol Phys*. 2009;73:1391-1396.
18. Nagakawa T, Kayahara M, Ohta T, et al. Patterns of neural and plexus invasion of human pancreatic cancer and experimental cancer. *Int J Pancreatol*. 1991;10:113-119.
19. Caravatta L, Sallustio G, Pacelli F, et al. Clinical target volume delineation including elective nodal irradiation in preoperative and definitive radiotherapy of pancreatic cancer. *Radiat Oncol*. 2012;7:86.
20. Makino I, Kitagawa H, Ohta T, et al. Nerve plexus invasion in pancreatic cancer: Spread patterns on histopathologic and embryological analyses. *Pancreas*. 2008;37:358-365.
21. Deshmukh SD, Willmann JK, Jeffrey RB. Pathways of extrapancreatic perineural invasion by pancreatic adenocarcinoma: Evaluation with 3D volume-rendered MDCT imaging. *AJR Am J Roentgenol*. 2010;194:668-674.
22. Mitsunaga S, Hasebe T, Kinoshita T, et al. Detail histologic analysis of nerve plexus invasion in invasive ductal carcinoma of the pancreas and its prognostic impact. *Am J Surg Pathol*. 2007;31:1636-1644.
23. Chatterjee D, Katz MH, Rashid A, et al. Perineural and intraneural invasion in posttherapy pancreaticoduodenectomy specimens predicts poor prognosis in patients with pancreatic ductal adenocarcinoma. *Am J Surg Pathol*. 2012;36:409-417.
24. 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;94:755-765.
25. 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;2:403-415.
26. 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;84:1166-1171.
27. Pollom EL, Alagappan M, von Eyben R, et al. Single- versus multifraction stereotactic body radiation therapy for pancreatic adenocarcinoma: Outcomes and toxicity. *Int J Radiat Oncol Biol Phys*. 2014;90:918-925.
28. Mahadevan A, Miksad R, Goldstein M, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. *Int J Radiat Oncol Biol Phys*. 2011;81:e615-e622.
29. Sun W, Leong CN, Zhang Z, et al. Proposing the lymphatic target volume for elective radiation therapy for pancreatic cancer: A pooled analysis of clinical evidence. *Radiat Oncol*. 2010;5:28.
30. Deki H, Sato T. An anatomic study of the peripancreatic lymphatics. *Surg Radiol Anat*. 1988;10:121-135.
31. Kayahara M, Nakagawara H, Kitagawa H, et al. The nature of neural invasion by pancreatic cancer. *Pancreas*. 2007;35:218-223.
32. Youl M, Hashem S, Brade A, et al. Induction gemcitabine plus concurrent gemcitabine and radiotherapy for locally advanced unresectable or resected pancreatic cancer. *Clin Oncol (R Coll Radiol)*. 2014;26:203-209.
33. Marchegiani G, Andrianello S, Malleo G, et al. Does size matter in pancreatic cancer?: Reappraisal of tumour dimension as a predictor of outcome beyond the TNM. *Ann Surg*. 2017;266:142-148.
34. Matsumoto G, Muta M, Tsuruta K, et al. Tumor size significantly correlates with postoperative liver metastases and COX-2 expression in patients with resectable pancreatic cancer. *Pancreatology*. 2007;7:167-173.
35. Fokas E, Eccles C, Patel N, et al. A treatment planning comparison of four target volume contouring guidelines for locally advanced pancreatic cancer radiotherapy. *Radiother Oncol*. 2013;107:200-206.
36. Baine MJ, Sleightholm R, Lin C. Incidence and patterns of locoregional failure after stereotactic body radiation therapy for pancreatic adenocarcinoma. *Pract Radiat Oncol*. 2019;9:e29-e37.
37. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817-1825.
38. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691-1703.
39. Jin G, Sugiyama M, Tuo H, et al. Distribution of lymphatic vessels in the neural plexuses surrounding the superior mesenteric artery. *Pancreas*. 2006;32:62-66.