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Survival benefit of adjuvant chemoradiotherapy for positive or close resection margin after curative resection of pancreatic adenocarcinoma

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ABSTRACT

Background: This study was conducted to identify patients who may benefit from adjuvant chemoradiotherapy (CRT) for positive or close resection margin (RM) after curative resection of pancreatic adenocarcinoma.

Methods: From 2004 to 2015, total of 472 patients with pancreatic adenocarcinoma underwent curative resection. After excluding patients with RM > 2 mm or unknown, remaining 217 patients were retrospectively analyzed. Forty-six (21.2%) patients were treated with adjuvant chemotherapy alone (CTx; mainly gemcitabine-based), 142 (65.4%) with adjuvant CRT (mainly upfront), and 29 (13.4%) patients didn't receive any adjuvant therapy (noTx group).

Results: Locoregional recurrence rate was significantly lower in the CRT group (43.7%) than in the CTx group (71.7%) or noTx group (65.5%) ($p = 0.001$). Significant survival benefits of CRT over CTx (HR 0.602, $p = 0.020$ for overall survival (OS); HR 0.599, $p = 0.016$ for time to any recurrence (TTR)) were demonstrated in multivariate analysis. CRT group had more 5-year survivors than other groups. In the subgroup analysis, such benefits of adjuvant CRT over CTx was observed only in patients with head tumor & vascular RM > 0.5 mm, but not in patients with body/tail tumor or vascular RM $\leq$ 0.5 mm. In the CRT group, radiation dose$\geq$54 Gy was significantly associated with better TTR and OS.

Conclusions: Adjuvant CRT could improve TTR and OS compared to adjuvant CTx alone in patients with close RM under 2 mm. Radiation dose escalation may be beneficial when feasible. Modern CRT regimen –based randomized evidence is needed for these high-risk patients.

Introduction

Pancreatic adenocarcinoma is and will be one of the major leading cause of cancer death worldwide [1]. Small proportion of patients can undergo resection with curative aim which is known as the only way to achieve long-term survival [2]. Even after curative resection, many patients could have microscopically positive or close resection margin (RM), and it is well known that survival for these so called R1 resection are pretty bad compared to margin cleared R0 resection [3].

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The definition of R1 resection has been a point of constant debate. College of American Pathologist (CAP) guidelines defined it as a microscopic presence of tumor cells at definite RM [4]. On the other hand, the Royal College of Pathologists in the UK suggested the '1 mm cutoff' for R1 resection [5]. However, it is difficult to judge whether a 1 mm cutoff, which is commonly used in rectal cancer, is also appropriate for pancreatic cancer because it has more infiltrative tendency therefore it is likely to underestimate microscopic extent. Some researchers suggested margin clearance of 1.5 mm or even up to 2 mm might be needed to obtain sufficient clinical benefit [6,7]. According to various criteria, the reported incidence of R1 resection varies widely among the reported studies, from 17% to >70% [8–11].

Meanwhile, various attempts to improve outcomes for resectable pancreatic cancer were not very progressive over the past few decades. Patients are more likely to recur distantly, although the risks of local recurrence also remain substantial even after R0 resection [12]. The optimal adjuvant treatment is still controversial because randomized comparisons of adjuvant chemotherapy (CTx) and chemoradiotherapy (CRT) are limited. The National Comprehensive Cancer Network guidelines recommend adjuvant CTx alone or induction CTx followed by CRT, regardless of RM status. Considering high risk for local recurrence especially for patients with positive or close RM, adjuvant radiotherapy (RT) in conjunction with chemotherapy can be considered preferred option. Unfortunately, no prospective studies have solely focused on these R1 patients; therefore, no optimal adjuvant treatment strategy of R1 resection has been established, which might be different and also should be distinguished from that of R0 resection.

Therefore, we reviewed our institutional experience to investigate the role of adjuvant CRT in patients with positive or close RM (equal or less than 2 mm), and to identify subgroup of patients who may benefit from adjuvant CRT over chemotherapy alone in these patients.

Methods

Study population

After obtaining institutional review board approvals (No. 2018-1478), we retrospectively searched for eligible patients from our single institutional database. Between Jan 2004 and Dec 2015, a total of 472 patients underwent curative resection for pancreatic adenocarcinoma. We excluded patients with all RM > 2 mm or unknown (n = 157), immediate recurrence after surgery during adjuvant treatment decision process (n = 17), double primary cancer (n = 8), and early follow-up loss less than 2 months (n = 51). To investigate appropriate adjuvant therapy option, patients receiving neoadjuvant treatment (n = 21) and adjuvant RT alone (n = 1) were further excluded. As a result, remaining 217 patients with 2 mm or closer RM subject to potential adjuvant therapy were included in this study (Supplemental Fig. 1).

Pancreatectomy with regional lymphadenectomy were performed by two experienced surgeons throughout the study period. The extent of adjacent vessel resection and anastomosis was determined by surgeons' discretion to obtain R0 resection. In patients undergoing portal vein or superior mesenteric vein partial resection due to suspicious tumor invasion into vessels, *en bloc* tumor resection with the involved vein and reconstruction in accordance with standard vascular techniques were performed. In case of vascular resection, vascular RM denoted the superior mesenteric artery RM. Detailed surgical procedures have been previously reported [13,14].

Pathologic characteristics of tumor specimens included tumor size, grade, RM in each direction (anterior, posterior, vascular, pancreas, bile duct, and duodenum), lymph node (LN) status, and lymphatic invasion (LI), venous invasion (VI), or perineural invasion (PNI) were obtained from a final pathology report. Positive RM (0 mm) was defined as the presence of tumor cell in any direction. Tumor and nodal status were re-classified using standard TNM staging, 8th edition.

Adjuvant treatments

Postoperative adjuvant CTx was basically applied to all patients unless contraindicated. Nonetheless, 29 (13.4%) patients didn't receive any adjuvant therapy (noTx) due to patient's refusal or poor performance status. Forty-six (21.2%) patients were treated with adjuvant CTx alone (34 patients with gemcitabine-based regimen, 12 patients with 5FU-based regimen). 142 patients underwent adjuvant CRT; 109 of them received upfront CRT with or without maintenance CTx and other 33 patients received 2 cycles of adjuvant gemcitabine plus cisplatin followed by CRT and then 4 cycles of maintenance gemcitabine based on the institutional prospective protocol. Adjuvant RT was delivered to the tumor bed and regional lymph node area mainly using 3D-conformal technique. The median total RT dose was 50.4 Gy (range, 12.6–55.8), with daily fractions of 1.8–2.0 Gy. Tumor bed boost (range, 5.4–10.8) was planned after 45 Gy to the regional nodal area. Representative radiation field of nodal area volume and boost volume was shown in Supplemental Fig. 2. Concurrent CTx regimen was 5-FU in 91 (64.1%) patients, gemcitabine in 44 (31.0%), and capecitabine in 7 (4.9%). All patients completed the planned RT except 5 patients. The median duration of RT was 41 days (range, 9–52).

Follow-up and statistical analysis

After the completion of each treatment, patients were followed up regularly. Abdominal computed tomography and/or ultrasonography and/or positron emission tomography were performed every 2–6 months or when clinically indicated. At the time of recurrence, various types of salvage treatment were performed according to the disease extent and physician's judgments.

Recurrence sites were classified as locoregional (around the remnant pancreas, surgical bed, anastomosis sites, or regional nodal), distant (liver, lung, peritoneum, bone, or others), or both. Overall survival (OS) was calculated from the date of surgery to the date of death from any cause or the last follow-up. Time to recurrence (TTR) was defined as the time interval between the date of surgery and any type of failure during the follow-up. Intergroup differences of the proportion in clinicopathologic factors were analyzed by Chi-square test. The OS and TTR were calculated through the Kaplan-Meier method and compared using the log-rank test. Factors with a p-value < 0.1 on univariate analysis or factors considered clinically important (e.g., CRT) were incorporated into the multivariate analysis with Cox proportional hazards model for calculating hazard ratios (HR) and 95% confidence intervals (CI). R statistical package (https://www.r-project.org/) was used for all statistical analyses.

Results

Patient characteristics and resection margin status

The characteristics of the patients included in this study are presented in Table 1. The median age was 65 years (range, 38–83). About two thirds of the patients (68.2%) had pancreas head tumor. Most patients underwent appropriate LN dissection with a median number of examined LN was 16 (interquartile range, 11–24). One hundred thirty-five (62.2%) patients had LN metastases and the

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Table 1
Overall patients' characteristics (N = 217).

		No.	%
Age at diagnosis		Median 65 (range, 38–83)	
Sex	Male	115	53.0
	Female	102	47.0
Op period	2004–2009	88	40.6
	2010–2015	129	59.5
Tumor location	Head	148	68.2
	Body/tail	69	31.8
Surgery	PPPD	100	46.1
	PD	46	21.2
	DP	66	30.4
	TP	5	2.3
Preoperative CA19-9	≤37	68	31.8
(U/ml)	>37	146	68.2
Postoperative CA19-9	≤37	161	79.3
(U/ml)	>37	42	20.7
Tumor grade	WD	18	8.3
	MD	180	83.0
	PD	19	8.8
T stage	T1	30	13.8
	T2	148	68.2
	T3	39	18.0
N stage	N0	82	37.8
	N1	96	44.2
	N2	39	18.0
RM_any (cm)		Median 0.1 (0–0.2)	
RM group	0 (RM = 0 mm)	32	14.8
	1 (0 < RM ≤ 1 mm)	129	59.5
	2 (1 < RM ≤ 2 mm)	56	25.8
RM_vas (cm)		Median 0.1 (0–1.3)	
RM_ant (cm)		Median 0.2 (0–1.9)	
RM_post (cm)		Median 0.2 (0–2.3)	
RM_pan (cm)		Median 1.0 (0–7.7)	
RM_bd (cm)		Median 3.0 (0–46.0)	
RM_duo (cm)		Median 3.5 (0.5–17.0)	
Lymphatic invasion	Yes	103	52.5
	No	114	47.5
Venous invasion	Yes	72	33.2
	No	145	66.8
Perineural invasion	Yes	185	85.3
	No	32	14.8
Adjuvant treatment	No adjuvant Tx	29	13.4
	Chemotherapy alone	46	21.2
	CRT	142	65.4

Op, operation; PPPD, pylorus-preserving pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; RM, resection margin; RM_ant, anterior RM; RM_pan, pancreatic parenchymal RM; RM_vas, vascular RM; RM_post, posterior RM; RM_bd, biliary RM; RM_duo, duodenal RM; Tx, treatment; CRT, chemoradiotherapy.

median number of positive LN was 2 (range, 1–13). Overall, median closest RM was 1 mm (range, 0–2). RM was classified as 0 mm in 32 (14.8%) patients, 0 < RM ≤ 1 mm in 129 (59.5%), and 1 < RM ≤ 2 mm in 56 (25.8%). There was no association between the above three RM group and the implemented type of adjuvant treatments ($p = 0.196$). Regarding the direction of margin, vascular RM had shortest median value of 1 mm, followed by anterior (median 2 mm), posterior (median 2 mm), and pancreas (median 10 mm). Histologic LI, VI, and PNI were identified in 103 (52.5%), 72 (33.2%), and 185 (85.3%) patients, respectively. The characteristics of the patients according to the adjuvant treatment groups are presented in Supplemental Table 1.

Patterns of failure, toxicities, and long-term survivors

The mean time to initiation of adjuvant treatment from surgery was 47 days (range, 21–94) in the CTx group and 46 days (range, 30–108) in the CRT group. On the other hand, mainly due to the recurrence during adjuvant treatment period, CTx group appears to have reduced treatment completion rates compared to CRT group (73.9% vs. 92.3%) because 6 cycles of adjuvant chemotherapy were approximately 3 times longer than upfront CRT. With a median follow-up period of 23 months (range, 3–170), 161 (74.2%) patients experienced recurrences. As a first site of failure, isolated locoregional recurrence (LRR) and distant metastasis (DM) developed in 40 (18.4%) and 70 (32.3%) patients, respectively. 51 (23.5%) patients developed both LRR and DM simultaneously. Most frequent DM site was the liver (n = 70). Other DM developed in the peritoneum (n = 35), lung (n = 23), bone (n = 8), and non-regional LN (n = 3). By dividing according to the adjuvant treatment groups, overall LRR rate was significantly lower in the CRT group (43.7%) than in the CTx group (71.7%) or noTx group (65.5%) ($p = 0.001$, Supplemental Table 1). However, DM rate was not significantly different among the three adjuvant treatment groups ($p = 0.454$). During follow-up period, grade 3 or higher gastrointestinal toxicity occurred in 2 (4.3%) patients in the CTx group (bleeding 1, obstruction 1) and 8 (5.6%) patients in the CRT group (bleeding 3, ulceration 2, obstruction 1, and anastomosis leakage 2). Overall, 169 (77.9%) patients died during follow-up period. Thirty-seven (17.1%) patients survived more than 5 years, 34 of whom were in CRT group (34/142, 23.9%), 1 was in CTx group (1/46, 2.2%), and 2 were in noTx group (2/29, 6.9%) ($p = 0.001$, Supplemental Table 1). Among these 37

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long-term survivors, 26 (70.3%) patients had no evidence of disease until last follow-up.

OS and TTR by clinicopathologic factors

The results of the univariate analyses for OS and TTR are listed in Table 2. Median OS and TTR for the entire patients were 26.1 months and 13.3 months, respectively.

On univariate analysis, postoperative CA19-9, vascular RM, and LI were identified as significant adverse prognosticators for both TTR and OS. Among various margin status, only the vascular RM showed a significant difference in outcome by dividing the median cutoff whereas pancreas RM or posterior RM did not. Type of adjuvant treatment was a significant prognostic factor for OS in univariate analysis, but not for TTR: 2-year TTR and OS for noTx, CTx, and CRT group were 27.7%, 24.0%, and 33.0% ($p = 0.370$, Fig. 1A) and 34.5%, 52.2%, and 57.8% ($p = 0.009$, Fig. 1B), respectively. CRT benefit over CTx was not clear in univariate analysis (Table 2).

However, we included adjuvant treatment factor into multivariate analysis model to adjust possible imbalances among treatment groups, as shown in the Supplemental Table 1. Multivariate analysis showed that adjuvant treatment was an independent prognostic factor for both TTR and OS along with postoperative CA19-9, vascular RM, and LI. Specifically, significant survival benefits of CRT over CTx (HR 0.602, $p = 0.020$ for OS; HR 0.599, $p = 0.016$ for TTR) were demonstrated. CTx alone had no advantage over noTx group in multivariate analysis for both TTR and OS (Table 2).

Additional univariate and multivariate analysis were performed after excluding patients without adjuvant treatment (Supplemental Table 2). It also showed similar results; significant benefits of CRT over CTx in TTR (HR 0.652, $p = 0.042$) and OS (HR 0.572, $p = 0.010$) were found.

Investigation of survival benefit of CRT according to each characteristic

After excluding patients without adjuvant treatment, subgroup analysis was performed to further identify patients with positive or close RM who could derive benefit from CRT compared to adjuvant CTx alone. Supplemental Fig. 3 plotted HR and 95% CI comparing OS according to the receipt of RT for each subgroup. Specifically, benefits of adjuvant CRT over CTx was observed in patients with head tumor (HR 0.564, $p = 0.016$) or vascular RM > 0.5 mm (HR 0.516,

Table 2
Analysis of time to recurrence (TTR) and overall survival (OS) in all patients (N = 217).

	No.	TTR			OS		
		2 y TTR (%)	Univariate p	Multivariate P, HR (95% CI)	2 y OS (%)	Univariate p	Multivariate p, HR (95% CI)
Age at diagnosis			0.079	0.047		0.877	
≤60	72	23.6		1	54.2		
>60	145	34.3		0.695 (0.485–0.995)	53.1		
Sex			0.342			0.066	0.151
Female	102	32.9			57.8		1
Male	115	28.5			49.6		1.283 (0.913–1.802)
Op period			0.343			0.261	
2004–2009	88	27.9			46.6		
2010–2015	129	32.5			58.1		
Tumor location			0.082	0.182		0.219	
Head	148	26.2		1	52.0		
Body/tail	69	39.8		0.761 (0.510–1.136)	56.5		
CA19-9 (postop)			<0.001	<0.001		<0.001	0.003
≤ 37 U/ml	161	37.2		1	60.3		1
>37 U/ml	42	7.5		2.474 (1.624–3.768)	31.0		1.856 (1.241–2.775)
Tumor grade			0.523			0.125	
WD/MD	198	30.9			54.6		
PD	19	27.9			42.1		
T stage (8th)			0.089	0.509		0.868	
T1-2	178	31.7		1	53.4		
T3	39	25.6		1.155 (0.753–1.771)	53.9		
N stage (8th)			<0.001	0.304		0.001	0.021
N0	82	45.7		1	69.8		1
N1-2	135	21.5		1.224 (0.833–1.799)	43.7		1.525 (1.065–2.183)
RM_pan			0.576			0.959	
≤1 cm	117	32.0			53.9		
>1 cm	90	30.2			55.6		
RM_vas			0.026	0.008		0.004	0.005
≤1 mm	127	27.0		1	47.2		1
>1 mm	73	34.7		0.613 (0.427–0.881)	64.4		0.590 (0.409–0.851)
RM_post			0.628			0.833	
≤2 mm	58	31.2			53.5		
>2 mm	38	23.2			55.3		
Lymphatic invasion			<0.001	<0.001		<0.001	0.003
No	114	44.1		1	64.0		1
Yes	103	15.9		1.985 (1.395–2.827)	41.8		1.660 (1.187–2.322)
Adjuvant Tx			0.370	0.016 (CRT) /0.425 (noTx)		0.009	0.020 (CRT) /0.629 (noTx)
Chemo alone	46	24.0		1	52.2		1
CRT	142	33.3		0.599 (0.395–0.909)	57.8		0.602 (0.392–0.925)
noTx	29	27.7		0.758 (0.384–1.497)	34.5		1.165 (0.627–2.166)

HR, hazard ratio; CI, confidence interval; Op, operation; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; RM, resection margin; RM_pan, pancreatic parenchymal RM; RM_vas, vascular RM; RM_post, posterior RM; Tx, treatment; CRT, chemoradiotherapy.

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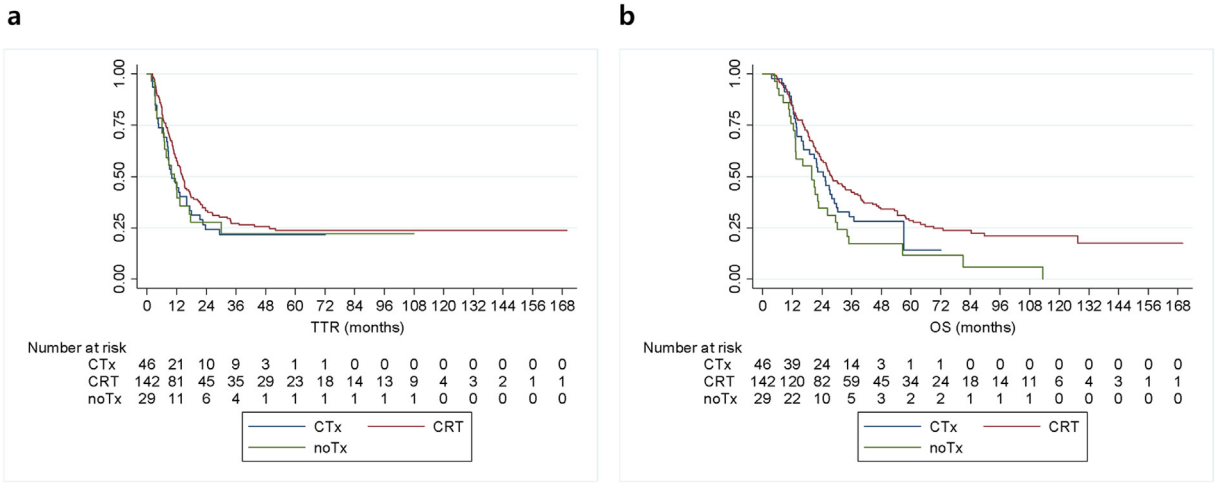

Fig. 1. Kaplan-Meier graphs of time to recurrence (TTR) (a) and overall survival (OS) (b) by adjuvant treatments in all study patients (N = 217).

p = 0.003). According to these factors, we stratified patients by having two factors or not. As a result, in patients with head tumor & vascular RM > 0.5 mm receiving adjuvant CTx (n = 123), CRT showed better TTR (HR 0.579, p = 0.026) and OS (HR 0.508, p = 0.010) than CTx alone (Fig. 2a and c). However, in patients with body/tail tumor or vascular RM ≤ 0.5 mm receiving adjuvant CTx (n = 77), TTR (HR 0.785, p = 0.495) and OS (HR 0.814, p = 0.547) were not different between CRT and CTx (Fig. 2b and d).

Impact of radiation dose on TTR and OS in patients receiving adjuvant CRT

Table 3 showed the univariate and multivariate analysis of TTR and OS in patients receiving adjuvant CRT (n = 142). Postoperative

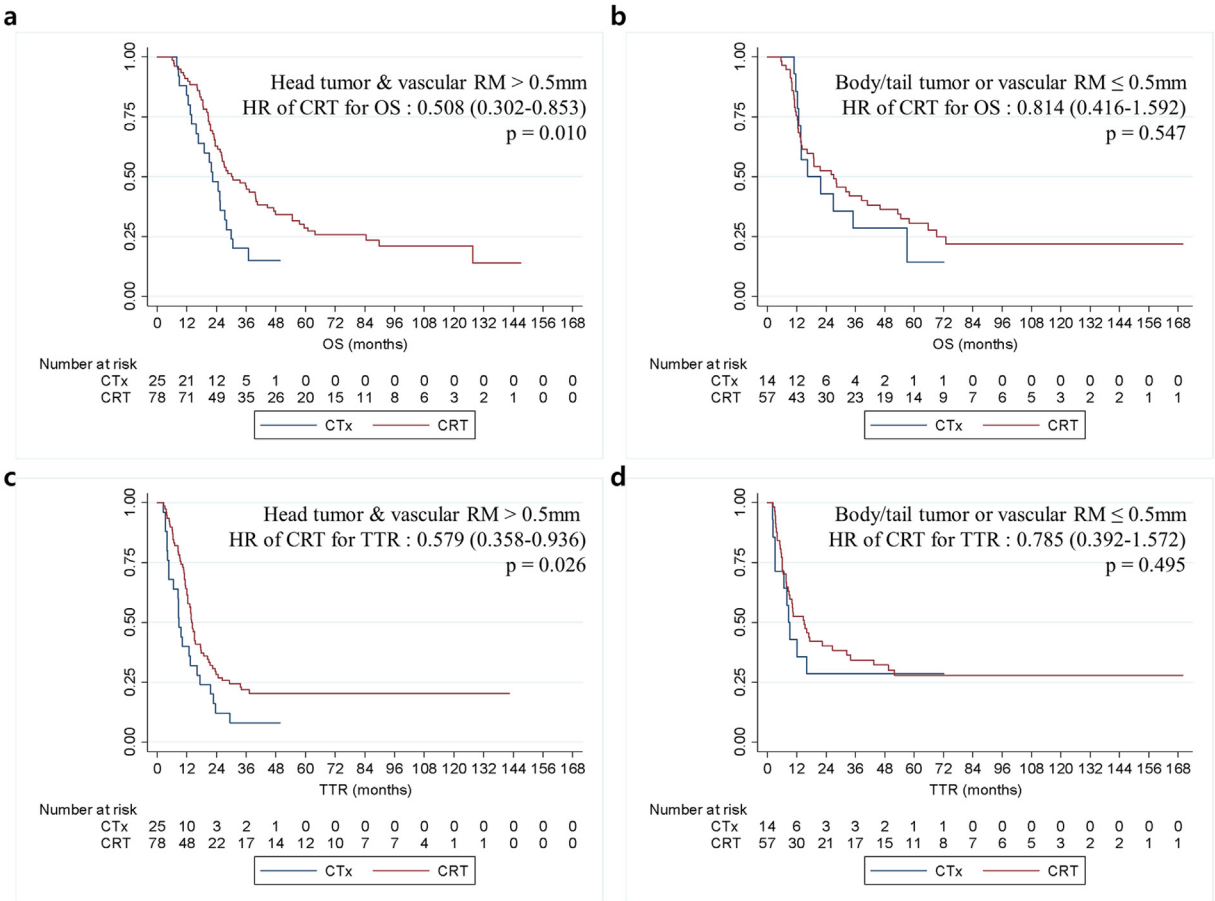

Fig. 2. Kaplan-Meier curves of overall survival (a) in patients with head tumor & vascular RM > 0.5 mm and (b) in patients with body/tail tumor or vascular RM ≤ 0.5 mm. Kaplan-Meier curves of time to recurrence (c,d) were also shown.

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Table 3
Analysis of time to recurrence (TTR) and overall survival (OS) in patients underwent adjuvant chemoradiotherapy (n = 142).

		TTR			OS		
	No.	2 y TTR (%)	Univariate p	Multivariate p, HR (95% CI)	2 y OS (%)	Univariate p	Multivariate p, HR (95% CI)
Age at diagnosis			0.159			0.735	
≤60	58	27.6			56.9		
>60	84	37.4			58.3		
Sex			0.427			0.096	
Female	72	35.3			58.3		
Male	70	31.3			57.1		
Op period			0.320			0.379	
2004–2009	67	28.3			52.2		
2010–2015	75	37.9			62.7		
Tumor location			0.191			0.944	
Head	92	28.2			59.8		
Body/tail	50	43.0			54.0		
CA19-9 (postop)			<0.001	<0.001		0.001	0.030
≤37 U/ml	108	39.6		1	63.0		1
>37 U/ml	29	11.1		2.282 (1.396–3.729)	37.9		1.723 (1.055–2.815)
Tumor grade			0.219			0.089	
WD/MD	132	34.3			59.1		
PD	10	20.0			40.0		
T stage (8th)			0.066	0.192		0.825	
T1-2	115	35.0		1	59.1		
T3	27	25.9		1.385 (0.849–2.257)	51.9		
N stage (8th)			0.002	0.431		0.015	0.461
N0	55	48.3		1	72.7		1
N1-2	87	23.8		1.200 (0.762–1.890)	48.3		1.185 (0.755–1.857)
RM_pan			0.250			0.462	
≤1 cm	82	37.7			58.5		
>1 cm	55	29.8			60.0		
RM_vas			0.122			0.009	0.051
≤1 mm	90	30.8			54.4		1
>1 mm	45	37.8			66.7		0.627 (0.392–1.002)
RM_post			0.558			0.628	
≤2 mm	33	34.3			60.6		
>2 mm	18	22.2			55.6		
Lymphatic invasion			<0.001	0.001		0.001	0.029
No	78	46.7		1	68.0		1
Yes	64	17.2		2.006 (1.318–3.053)	45.3		1.605 (1.049–2.456)
Radiation dose*			0.003	0.012/0.002		0.001	0.163/0.021
<50 Gy	24	12.5		1	33.3		1
50–50.4 Gy	82	33.2		0.508 (0.300–0.860)	58.5		0.673 (0.386–1.174)
54–55.8 Gy	36	47.1		0.372 (0.196–0.705)	72.2		0.453 (0.232–0.886)

*50–50.4 Gy vs. 54–55.8 Gy univariate p = 0.285 (TTR)/p = 0.152 (OS).
HR, hazard ratio; CI, confidence interval; Op, operation; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; RM, resection margin; RM_pan, pancreatic parenchymal RM; RM_vas, vascular RM; RM_post, posterior RM.

high CA19-9, and LI showed significant association on both outcomes, as above. Especially, radiation dose was found to be a significant factor for TTR (p = 0.003) and OS (p = 0.001). Specifically, radiation dose ≥54 Gy showed significantly better TTR (HR 0.372, p = 0.002) and OS (HR 0.453, p = 0.021) compared to dose<50 Gy after multivariate adjustments (Table 3). Kaplan-Meier curves of TTR and OS based on adjuvant radiation dose showed different prognosis between three dose groups (Fig. 3). The characteristics of the patients according to the radiation dose groups are presented in Supplemental Table 3. The outcomes of patients who underwent upfront CRT (n = 109) were not significantly different from those of who underwent CTx followed by CRT (n = 33) (data not shown).

Discussion

The potential benefit of adding RT to CTx and its use in the adjuvant setting of pancreatic cancer remain controversial. Moreover, non-standardized pathologic report and different definition of R1 RM made it difficult to analyze the impact of adjuvant therapy based on the RM status. Nonetheless, many reports consistently supported differential prognosis based on R1 status, recommendation stratified by RM is warranted [15]. One previous meta-analysis of randomized adjuvant trials demonstrated that HR of adjuvant CRT on survival in R1 patients was 0.72 compared with 1.19 in R0 patients [11]. It was also reported that HR of adjuvant CTx in R1 patients was 1.04 compared with 0.65 in R0 patients which might suggest that CTx alone was not beneficial in R1 patients [11]. More recent updated meta-analysis showed that there was no significant difference in OS with adjuvant CRT (HR 1.09) in all patients, but subgroup analyses estimated that adjuvant CRT (HR 0.72) but not CTx (HR 0.96) was more effective in patients with positive RM, which was fairly corresponded with our results as well as previous meta-analysis [16].

To further investigate specific indications, we did a subgroup analysis to answer the question of which patients derived most benefit from adjuvant CRT in R1 subset. It showed that CRT improved OS among patients with head tumor and having at least sufficient vascular RM (>0.5 mm) whereas CRT did not confer an OS benefit among patients with body/tail tumor, or those with narrow vascular RM. The impact of different involved RM has been investigated and revealed that significantly poor survival in patients with positive vascular RM compared to anterior or posterior RM [17,18]. However, previous data about the impact of vascular RM in patients received adjuvant CRT are scarce. It is likely that there was

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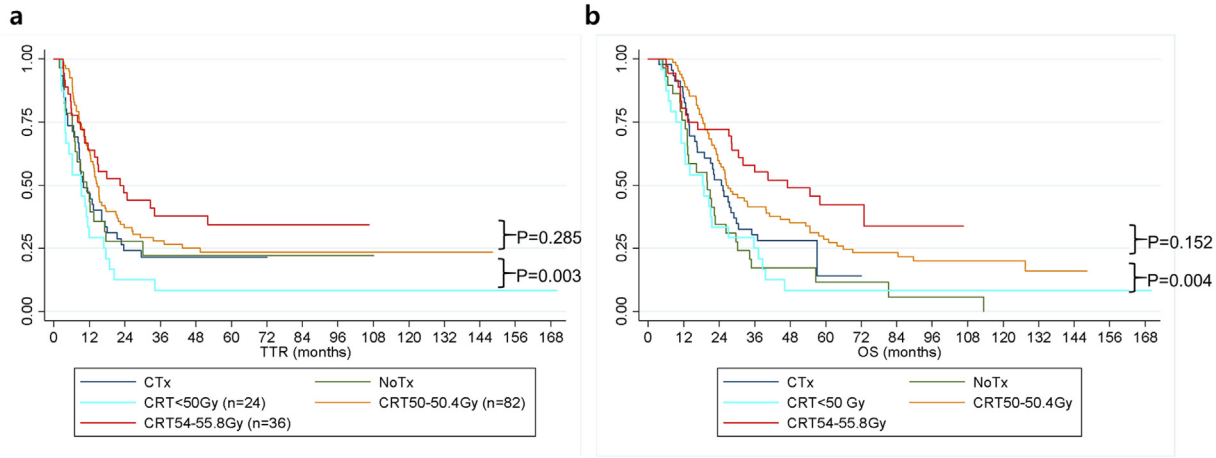

Fig. 3. Kaplan-Meier graphs of time to recurrence (TTR) (a) and overall survival (OS) (b) by adjuvant treatment and radiation dose groups in all study patients.

no benefit of RT addition because such patients had much remnant local tumor burden and also an increased risk of DM therefore an expected benefit of locoregional control might not extend to OS benefit. Researchers from University of Pittsburgh analyzed the impact of adjuvant CRT based on RM extent after pancreaticoduodenectomy [19]. On their margin-stratified analysis, adjuvant CRT was significantly associated with OS in RM $\leq$ 1 mm (HR 0.36; p = 0.002) but not for RM = 0 mm (HR 0.65, p = 0.15) and RM > 1 mm (HR 0.74, p = 0.46). In addition, the reason why adjuvant CRT was more beneficial for the patients with head tumor as shown in our subgroup analysis is difficult to interpret due to scarcity of previous reports. Since LRR rate was significantly higher in the pancreatic head tumor than in the body/tail tumor in our patients (58.1% vs. 40.6%, p = 0.024), it might affect the magnitude of survival benefit of adjuvant CRT in head tumor subgroup. However, the current data alone is limited to interpret the exploratory results of subgroup analysis and further studies are needed.

In our study, overall poor outcomes suggested that not all close RM could be fully rescued by adjuvant CRT. Considering the high R1 resection rate based on resectable or borderline resectable criteria, neoadjuvant treatments might have benefit of increasing R0 rates in some cases, especially to the threatened vascular RM. Another recent systematic review for resectable pancreatic cancer suggested that neoadjuvant therapy may be preferred with clinical benefit over upfront surgery with adjuvant therapy [20]. However, analyzed cohort excluded patients who underwent neoadjuvant therapy, thus, it is beyond the scope of this study and several trials are being awaited.

Still, few other individual studies have investigated a role of CRT in R1 patients. Osipov et al. suggested that RM up to 2 mm was an independent predictor of local recurrence-free survival, disease-free survival, and OS (HR 0.31, p = 0.008) [21]. Divided by adjuvant treatments, RM > 2 mm was still prognostic for OS in patients with adjuvant CTx (p = 0.03) whereas it was not significantly prognostic in patients with adjuvant CRT (p = 0.19). It might indicate that adjuvant CRT mitigated the prognostic impact of RM, therefore authors recommended adjuvant CRT for RM up to 2 mm. In other study using a large national database (National Cancer Data Base (NCDB)), Rutter et al. demonstrated that adjuvant CRT was independently associated with improved OS for all resected pancreatic adenocarcinoma [22]. Interestingly, CRT compared to CTx alone was associated with improved OS in both R0 resection (HR, 0.901; p = 0.005) and R1 resection (HR, 0.842; p = 0.030). Recent more updated analysis from NCDB, Takahashi et al. showed adjuvant CRT but not adjuvant CTx improved survival in the R1/LN negative (p < 0.004), and LN positive (p < 0.001) [23]. Adjuvant CTx augmented OS only in R1/LN positive (p < 0.001). They concluded that survival benefits were greater in those receiving adjuvant CRT for R1 resected patients. Generally, previous retrospective studies, meta-analysis, and our results strongly supported the incorporation of adjuvant RT for R1 patients, although the definition of R1 varies from study to study. However, previous studies did not analyze R1 patients in more detail by the type of close or positive margin. As we firstly suggested in the subgroup analysis, not all R1 patients may have consistent CRT benefits. Although it is difficult to conclude whether there is really no significant benefit in patients with body/tail tumor or vascular RM $\leq$ 0.5 mm, future studies should account for detailed RM status or tumor location when assessing the impact of adjuvant CRT.

One of the interesting finding of the present study is an association between adjuvant radiation dose and survival. Patients receiving high doses of adjuvant RT showed a significantly improved TTR and OS (Fig. 3). Although some imbalance of characteristics existed, multivariate analysis also revealed the significant impact of higher dose, which suggested that radiation dose $\geq$54 Gy could be considered when feasible. Few studies evaluated the impact of radiation dose in the setting of adjuvant CRT in pancreatic cancer. When not using 3D conformal RT technique, Abrams et al. reported no significantly different outcomes for the low dose group (up to 50.4 Gy to the tumor bed) and the high dose group (up to 57.6 Gy to the tumor bed) with only 29 patients of pancreatic and periampullary adenocarcinoma [24]. But recently, Morganti et al. reported their multicenter data of 514 patients with macroscopically negative RM and demonstrated that the median survival of each adjuvant RT doses of <45 Gy, 45–50 Gy, 50–55 Gy, and $\geq$55 Gy was 13, 21, 22, and 28 months, respectively (p = 0.004) [25]. Together with our results, these relationship between radiation dose and OS supports indirectly the important role of RT in resected pancreatic cancer, especially for R1 patients. Furthermore, the use of modern RT techniques in the experienced center could enable safe administration of high-dose RT without increasing severe toxicities [26]. New RT target volume smaller than standard have also been suggested to allow dose escalation while minimizing RT toxicities [27]. In the era of intensity modulation RT, new evidences will be needed to re-establish the role of the adjuvant CRT with escalated dose for these high-risk patients.

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One of the strengths of current study is relatively homogeneous pathologic evaluation analysis performed at a single institution. However, a number of limitations need to be addressed. First, its retrospective nature is the major flaw that study patients were not randomized, and sources of bias were therefore not fully controlled for. Second, the heterogeneity of the CRT regimens could also affect treatment outcomes. Lastly, a small number of patients in the CRT group made it difficult to clearly show the statistical differences by radiation dose escalation. Considering above limitations, prospective trials using modern CRT regimen for R1 disease are required to validate our results.

As the paradigm of adjuvant treatment continues to evolve, the role of adjuvant RT may become increasingly difficult to answer. Although aggressive CTx regimens such as modified FOLFIRINOX or gemcitabine combined with capecitabine yield more favorable survival recently, not all patients are suitable for this toxic regimens after surgery and also these regimens are not yet covered by national insurance system in many countries [28,29]. As more effective CTx will be introduced, the importance of locoregional control should become increasingly gain attention. Our real-world results can also be used as a reference data for applying individualized RT in patients receiving up-to-date CTx.

In conclusion, adjuvant CRT significantly improved clinical outcomes compared to adjuvant CTx alone in patients with RM $\leq$ 2 mm. Radiation dose escalation may be beneficial when feasible. Modern CRT regimen–based randomized evidence is needed for these high-risk patients. In addition, further research on the impact of vascular RM and tumor location are also needed to clarify the subset of resected pancreatic cancer patients likely to have significant benefit from adjuvant CRT.

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CRediT authorship contribution statement

Byoung Hyuck Kim: Methodology, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Kyubo Kim:** Conceptualization, Investigation, Writing - review & editing, Supervision. **Jin-Young Jang:** Investigation, Resources, Writing - review & editing. **Wooil Kwon:** Investigation, Writing - review & editing. **Hongbeom Kim:** Investigation, Writing - review & editing. **Kyung-Hun Lee:** Investigation, Writing - review & editing. **Do-Youn Oh:** Investigation, Writing - review & editing. **Haeryoung Kim:** Investigation, Resources, Writing - review & editing. **Kyung Bun Lee:** Investigation, Resources, Writing - review & editing. **Eui Kyu Chie:** Conceptualization, Investigation, Writing - review & editing, Supervision.

Declaration of competing interest

None.

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Appendix A. Supplementary data

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