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Is 6 Months the Optimal Duration of Adjuvant Chemotherapy for Pancreatic Cancer?

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Abstract. *Aim: This study evaluated the relationship between the relative dose intensity (RDI) and the prognosis to assess the optimal duration of adjuvant chemotherapy for pancreatic cancer. Patients and Methods: From 2013 to 2018, 119 patients with pancreatic cancer underwent radical surgery. After excluding five patients who underwent R2 resection, three with stage IV disease, and two with adjuvant chemotherapy other than S-1, 109 cases were evaluated. They were classified into four groups based on the RDI for the total dosage of S-1: group 1: <50%, group 2: 50% to <80%, group 3: 80% to ≤125%, and group 4: >125%. Results: The number of patients in each group were 48, 20, 30 and 11, with median ages of 74, 73, 66 and 74, respectively. Median estimated glomerular filtration rate was 75, 72, 89 and 77 ml/min/1.73 m^2, respectively, demonstrating statistically significant differences. The corresponding median and 5-year overall survival rates were: 378 days and 17.9%; 1,011 days and 35.1%; 1,246 days and 41.6%; 1,389 days and 10.6%. Using group 1 as a reference, the adjusted hazard ratio was 0.39 for group 2, 0.36 for group 3, and 0.30 for group 4; all were statistically significant. Conclusion: The higher the RDI of S-1 in adjuvant chemotherapy, the better the overall survival. Therefore, 1 year of adjuvant chemotherapy with S-1 in pancreatic cancer may be preferable to 6 months.*

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The CONKO-001 trials, conducted mainly in Germany, have shown that adjuvant chemotherapy with gemcitabine for 6 months for pancreatic cancer prolongs survival better than surgery alone (1). Furthermore, the JASPAC-01 trial conducted in Japan showed that adjuvant chemotherapy with S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) for 6 months for pancreatic cancer prolonged survival longer than did gemcitabine therapy (2); the standard adjuvant chemotherapy for pancreatic cancer in Japan is S-1 therapy for 6 months.

On the other hand, regarding adjuvant chemotherapy for gastric cancer, the ACTS-GC trial showed that adjuvant chemotherapy with S-1 for 1 year improved survival in comparison to surgery alone in patients with stage II/III gastric cancer undergoing radical surgery (3), and S-1 therapy for 1 year has become the standard adjuvant therapy for gastric cancer. Subsequently, the JCOG1104/OPAS-1 trial was conducted to determine whether it was appropriate to shorten the treatment period to 6 months for patients with stage II only, as there was no scientific evidence to support a 1-year treatment period. However, the results showed that shortening the duration of treatment was associated with significantly worse outcomes in comparison to the standard treatment period of 1 year (4).

Pancreatic cancer has a poorer prognosis than gastric cancer, and it can be inferred that 1 year of adjuvant chemotherapy treatment is also preferable for pancreatic cancer. In clinical practice, it was anticipated that variations in the single dose of adjuvant chemotherapy and the duration

of treatment interruptions would be included. For this reason, it was determined that a correct evaluation of the optimal duration of adjuvant chemotherapy for pancreatic cancer cannot be made by examining the duration of treatment alone. However, there is an upper limit to a single dose of chemotherapy. Thus, increasing the actual dose relative to the standard treatment dose requires extending the duration of treatment. Therefore, there is a general correlation between the relative dose intensity (RDI) and the duration of treatment. The aim of this study was to retrospectively evaluate the relationship between the RDI of adjuvant chemotherapy and the prognosis in pancreatic cancer, and to assess the appropriate duration of adjuvant chemotherapy for pancreatic cancer.

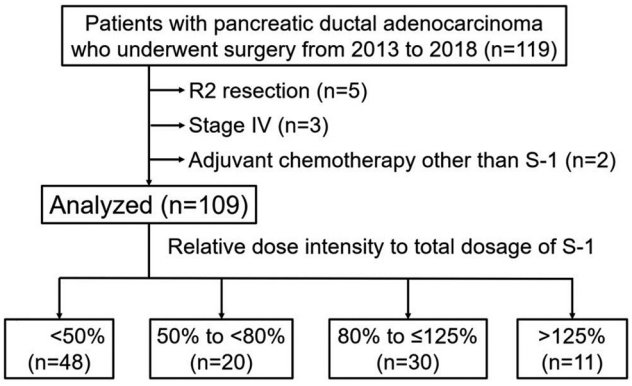


Figure 1. *Flow chart of the study.*

Patients and Methods

Study design. This was a single-center, retrospective, observational study. All data were retrospectively gathered from patients with pancreatic ductal adenocarcinoma who underwent radical surgery at Hyogo Medical University Hospital during the period from January 2013 to December 2018. Cases with R2 resection, stage IV cases, and cases that received adjuvant chemotherapy other than S-1 therapy were excluded.

Since this study used only data collected from medical records, informed consent was not obtained. However, an information disclosure statement about the study's implementation was published on the website, providing the opportunity for patients to opt out. All study protocols were approved by the Ethics Committee of Hyogo Medical University (approval number: 3968), and all procedures were conducted in accordance with the Declaration of Helsinki of 1964.

The daily dose of S-1 was determined based on the body surface area (BSA) (BSA <1.25m^2: 80 mg/day; BSA 1.25-1.50m^2: 100 mg/day; BSA >1.50m^2: 120 mg/day). The BSA was calculated using the Du Bois formula (5) based on the patient's height and weight at the time of discharge after surgery. Standard adjuvant chemotherapy with S-1 was set at four courses of 28 consecutive days of oral administration and 14 days of rest, and the RDI was calculated using the actual total dose of S-1. Since a half-dose is 50%, a one-step dose reduction is 80%, and an additional one-course dose is 125%, the patients were classified into four groups according to the RDI: Group 1: <50%; group 2: 50% to <80%; group 3: 80% to ≤125%; and group 4: >125%, and their long-term outcomes were compared.

Pancreatic cancer treatment in practice. In those days, there was no evidence to support the benefit of neoadjuvant chemotherapy for pancreatic cancer, and upfront surgery was the basic policy. However, some patients received neoadjuvant chemotherapy with gemcitabine plus S-1 or gemcitabine plus nab-paclitaxel because they were participating in a clinical study of neoadjuvant chemotherapy. All patients with pancreatic cancer underwent laparotomy. The basic surgical procedures were pancreaticoduodenectomy for pancreatic head cancer, distal pancreatectomy for pancreatic body/tail cancer, total pancreatectomy for pancreatic cancer spreading to three regions, and remnant total pancreatectomy for remnant pancreatic cancer. There were some cases in which a reduction operation was performed in consideration of the patient's general condition. In principle, adjuvant chemotherapy was to be started by postoperative week 12.

Predicted confounding factors. S-1 therapy may not be completed in elderly patients or patients with renal dysfunction. In addition, adjuvant chemotherapy may be administered for a longer period of time in patients with an R1 operation or a more advanced stage. Therefore, age, estimated glomerular filtration rate (eGFR), final stage and R0 resection were considered to be the most important factors in the analysis. In analyses, the relative hazards were adjusted for these confounding factors.

Definitions. The primary outcome was overall survival (OS) in four groups classified by RDI. OS was defined as the time from the date of surgery to death from any cause, and patients were censored at the date of the final confirmation of survival for surviving patients, or, for patients lost to follow-up, at the date of the final confirmation of survival before being lost to follow-up. The secondary outcome was relapse-free survival (RFS). RFS was the time from the date of surgery to the date of relapse or death from any cause.

Postoperative pancreatic fistula was defined in accordance with the Clavien-Dindo classification and the International Study Group of Pancreatic Fistula criteria (6). Perioperative complications with Clavien-Dindo classification of grade III or more were taken into consideration. The stage of cancer was determined in accordance with the eighth edition of the Union for International Cancer Control classification (7).

Statistical analysis. Continuous variables are presented as the median and interquartile range unless otherwise noted. Categorical variables are expressed as numbers and percentages. Comparisons were performed using the Kruskal-Wallis test for continuous variables, and the chi-square test for categorical variables. OS and RFS were estimated using the Kaplan-Meier method, and the log-rank method was used for between-group comparisons. The hazard ratio was calculated by Cox's proportional hazards model.

Results

Patient background factors, perioperative outcomes, and pathological findings. Between 2013 and 2018, 119 patients underwent surgical treatment. Excluding five patients with

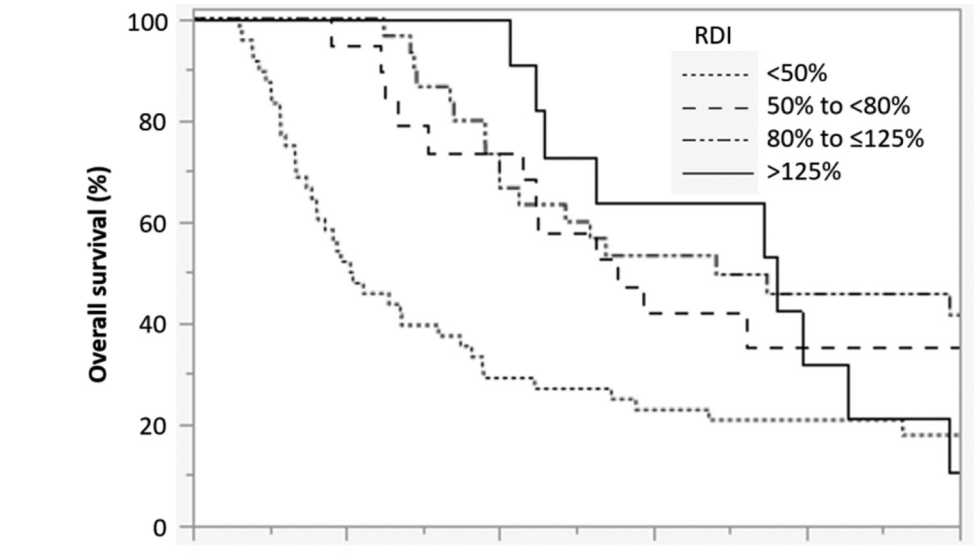
Table I. *Comparison of the background factors, perioperative outcomes and pathological findings in the four relative dose intensity (RDI) groups.*

Parameter		RDI group				*p*-Value
		<50% (n=48)	50% to <80% (n=20)	80% to ≤125% (n=30)	>125% (n=11)	
Background						
Age, years	Median (IQR)	74 (67-78)	73 (66-80)	66 (52-73)	74 (63-77)	**0.0037**
Sex, n (%)	Male	37 (77.1%)	15 (75.0%)	17 (56.7%)	8 (72.7%)	0.26
	Female	11 (22.9%)	5 (25.0%)	13 (43.3%)	3 (27.3%)	
BMI, kg/m^2	Median (IQR)	20.8 (19.2-23.7)	21.1 (20.4-22.8)	21.1 (19.9-22.7)	20.9 (19.2-22.1)	0.85
ASA-PS, n (%)	1	0 (0%)	1 (5.0%)	1 (3.3%)	1 (9.1%)	
	2	34 (70.8%)	10 (50.0%)	24 (80.0%)	6 (54.5%)	0.19
	3	14 (29.2%)	9 (45.0%)	5 (16.7%)	4 (36.4%)	
Neoadjuvant chemotherapy	Yes	6 (12.5%)	3 (15.0%)	4 (13.3%)	2 (18.2%)	0.96
Hemoglobin, g/dl	Median (IQR)	12.1 (11.2-13.6)	12.2 (11.2-12.8)	12.8 (11.8-13.9)	12.9 (12.2-13.2)	0.40
Albumin, g/dl	Median (IQR)	3.6 (3.3-3.9)	4.0 (3.5-4.2)	3.8 (3.5-3.9)	3.6 (3.4-4.0)	0.14
Total bilirubin, mg/dl	Median (IQR)	0.7 (0.5-1.0)	0.8 (0.5-1.1)	0.7 (0.6-1.1)	1.0 (0.8-1.8)	0.37
eGFR, ml/min/1.73 m^2	Median (IQR)	75 (57-91)	72 (64-91)	89 (77-111)	77 (59-85)	**0.03**
CA19-9, U/ml	Median (IQR)	92.0 (24.9-263)	86.9 (43.9-347)	60 (11.3-155)	63.8 (37.2-208)	0.46
Diameter of tumor, mm	Median (IQR)	26 (23-32)	23 (18-26)	24 (18-30)	26 (23-27)	0.21
Resectability, n (%)	R	39 (81.3%)	17 (85.0%)	25 (83.3%)	9 (81.8%)	0.18
	BR-PV	6 (12.5%)	0 (0%)	1 (3.3%)	0 (0%)	
	BR-A	1 (2.1%)	3 (15.0%)	4 (13.3%)	2 (18.2%)	
	UR-LA	2 (4.2%)	0 (0%)	0 (0%)	0 (0%)	
Perioperative outcomes						
Surgery, n (%)	PD	26 (54.2%)	10 (50.0%)	17 (56.7%)	7 (63.6%)	0.86
	DP	17 (35.4%)	9 (45.0%)	9 (30.0%)	3 (27.3%)	
	TP	3 (6.3%)	1 (5.0%)	3 (10.0%)	1 (9.1%)	
	rTP	0 (0%)	0 (0%)	1 (3.3%)	0 (0%)	
	Other	2 (4.2%)	0 (0%)	0 (0%)	0 (0%)	
Vascular resection, n (%)	Yes	11 (22.9%)	3 (15.0%)	5 (16.7%)	1 (9.1%)	0.68
Operation time, min	Median (IQR)	578 (445-691)	527 (367-653)	530 (420-627)	637 (555-679)	0.24
Blood loss, ml	Median (IQR)	735 (330-1,398)	723 (313-913)	435 (263-710)	835 (230-1,050)	0.38
Transfusion, n (%)	Yes	16 (33.3%)	5 (25.0%)	5 (16.7%)	4 (36.4%)	0.36
Perioperative complications	Clavien-Dindo ≥III	12 (33.3%)	11 (68.8%)	6 (35.3%)	2 (28.6%)	0.08
POPF, n (%)	Grade B	15 (31.3%)	10 (50.0%)	7 (23.3%)	3 (27.3%)	0.25
Postoperative hospital stays, days	Median (IQR)	31 (22-46)	38 (26-51)	27 (22-35)	30 (21-38)	0.22
Pathological findings						
Final stage, n (%)	IA	6 (12.5%)	4 (20.0%)	6 (20.0%)	1 (9.1%)	0.52
	IB	7 (14.6%)	4 (20.0%)	3 (10.0%)	0 (0%)	
	IIA	3 (6.3%)	0 (0%)	0 (0%)	0 (0%)	
	IIB	19 (39.6%)	10 (50.0%)	15 (50.0%)	6 (54.5%)	
	III	13 (27.1%)	2 (10.0%)	6 (20.0%)	4 (36.4%)	
pStage, n (%)	≥IIB	32 (66.7%)	12 (60.0%)	21 (70.0%)	10 (90.9%)	0.34
Resection, n (%)	R0	42 (87.5%)	17 (85.0%)	29 (96.7%)	8 (72.7%)	0.19

ASA-PS: American Society of Anesthesiologists Physical Status; BMI: body mass index; CA19-9: carbohydrate antigen 19-9; DP: distal pancreatectomy; eGFR: estimated glomerular filtration rate; IQR: interquartile range; PD: pancreaticoduodenectomy; POPF: postoperative pancreatic fistula; rTP: remnant total pancreatectomy; TP: total pancreatectomy. Statistically significant *p*-values ($p<0.05$) are shown in bold.

R2 resection, three patients with stage IV disease, and two patients with adjuvant chemotherapy other than S-1 therapy, 109 patients were included in the study. The patients were classified, according to RDI, as follows: Group 1, 48 patients; group 2, 20 patients; group 3, 30 patients; and group 4, 11 patients (Figure 1).

The following patient background factors were compared among the four groups: age, sex, body mass index, American Society of Anesthesiologists physical status, neoadjuvant chemotherapy, hemoglobin level, albumin level, total bilirubin level, eGFR values, CA19-9 level, tumor size, and resectability classification. Statistically significant



Number at risk						
RDI<50%	48	26	15	12	9	6
50% to <80%	20	19	15	9	6	4
80% to ≤125%	30	30	22	17	13	11
>125%	11	11	11	8	4	2

Figure 2. *Overall survival rates of the four relative dose intensity (RDI) groups.*

differences in age and eGFR values were observed. The patients in group 3, who completed standard adjuvant chemotherapy, were younger and had higher eGFR values (Table I).

The following perioperative outcomes were compared: Surgical procedure, rate of vascular resection, operative time, intraoperative blood loss, intraoperative blood transfusion, incidence of perioperative complications Clavien-Dindo grade ≥III, incidence of postoperative pancreatic fistula, and postoperative hospital stay, but no statistically significant differences were found (Table I).

Regarding postoperative pathological findings, the final stage and rate of R0 resection were compared, and there were no obvious statistically significant differences among the four groups. The percentages of cases with stage ≥IIB disease were also compared, and no statistically significant differences were found. However, the R0 resection rate was as high as 96.7% in group 3, and the percentage of patients with stage ≥IIB disease as high as 90.9% in group 4 (Table I).

OS and RFS. Survival curves representing OS and RFS, as determined using the Kaplan-Meier method, are shown in Figure 2 and Figure 3. The specific values are summarized in Table II.

With regard to the median survival time (MST), MST increased with increasing RDI, as follows: 378, 986, 1,143 and 1,361 days for groups 1 to 4, respectively. The corresponding 1-year survival rates were as follows: 52.1%, 94.7% 100% and 100%. The 3-year survival rates were 22.9%, 42.1%, 53.3% and 63.6%, respectively. As for the MST, the 1- and 3-year survival rates also increased as the RDI increased. The 5-year survival rates were 17.9%, 35.1%, 41.6% and 10.6%, respectively; the 5-year survival rate was lowest in group 4 patients. The log-rank method was used to compare OS among the four groups, and the *p*-value was 0.003, indicating a statistically significant difference.

With regard to the median RFS, it also increased with the RDI, with durations of 207, 386, 3,633 and 771 days, respectively. The 1-year RFS rates for the four groups were as follows: 38.9%, 50.0%, 76.7% and 100%, respectively. The corresponding 5-year RFS rates were 20.7%, 30.0%, 32.7% and 36.4%. However, the 3-year RFS rates were 20.7%, 30.0%, 40.0% and 36.4%, with a reversal between groups 3 and 4. The *p*-value for differences in the RFS rates, as calculated by the log-rank method, was 0.051.

Cox proportional hazards analysis. Table III shows the results of the hazard ratio calculations for OS and RFS.

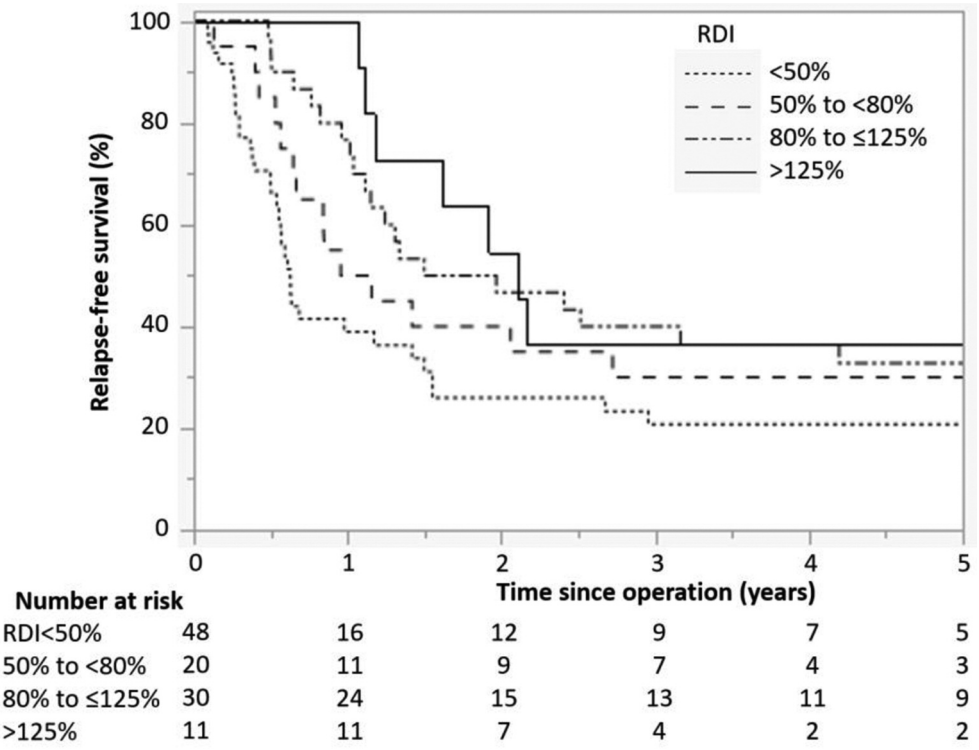


Figure 3. *Relapse-free survival rates of the four relative dose intensity (RDI) groups.*

Using group 1 as a reference, the hazard ratios for OS were as follows: group 2, 0.49; group 3, 0.42; and group 4, 0.48. All differences were statistically significant. The corresponding hazard ratios for RFS, using group 1 as a reference, were 0.71, 0.51 and 0.44; only that for group 3, *i.e.* that with an RDI of 80% to ≤125%, was statistically significantly lower.

As described in the Patients and Methods section, age, eGFR, final stage, and R0 resection rate were considered potential confounding factors for adjuvant chemotherapy. Therefore, the hazard ratios were calculated by adjusting for these factors. For OS, the adjusted hazard ratio decreased with each increase in RDI, as follows: group 2, 0.39; group 3, 0.36; and group 4, 0.30, and all values were statistically significant. The corresponding hazard ratios for RFS, after adjustment for confounding factors, were 0.74, 0.42 and 0.32. Although statistical significance was found only for groups 3 and 4, the hazard ratio was found to decrease with each increase in RDI.

Discussion

In the present study, we retrospectively analyzed the long-term outcomes at our Institution under the assumption that the longer the duration of adjuvant chemotherapy for pancreatic cancer, the better the long-term outcomes. However, it is unlikely that a good therapeutic effect can be achieved with the long-term administration of a low dose. Therefore, we decided to evaluate the duration of adjuvant chemotherapy from the perspective of the RDI. The practical analysis confirmed that the higher the RDI, the lower the hazard ratio for both OS and RFS; the higher the RDI, the better the OS and RFS.

A high RDI is not the same as a long duration of treatment with postoperative adjuvant chemotherapy. Even if adjuvant chemotherapy should be longer than 6 months, it is not clear whether it should be 1, two, or 5 years. However, our results would suggest that 1 year of adjuvant chemotherapy for pancreatic cancer might be better than 6 months.

Various studies have been conducted on adjuvant therapy for pancreatic cancer. The ESPA-01 trial compared four groups of patients treated with surgery alone, surgery with adjuvant chemotherapy, surgery with adjuvant chemoradiotherapy, or surgery with adjuvant chemotherapy plus chemoradiotherapy, and reported that adjuvant chemoradiotherapy had a deleterious effect on survival (8). The CONKO-001 trial reported for the first time that postoperative adjuvant chemotherapy improved both OS and RFS more than surgery alone. In the CONKO-001 trial, gemcitabine was administered as postoperative adjuvant

Table II. *Overall survival (OS) and relapse-free survival (RFS) of the four relative dose intensity (RDI) groups.*

	RDI group	Median time, days (n=48)	Rate at 1 Year (n=20)	Rate at 3 Years (n=30)	Rate at 5 Years (n=11)
OS	<50%	378	52.1%	22.9%	17.9%
	50% to <80%	986	94.7%	42.1%	35.1%
	80% to ≤125%	1143	100.0%	53.3%	41.6%
	>125%	1361	100.0%	63.6%	10.6%
RFS	<50%	207	38.9%	20.7%	20.7%
	50% to <80%	386	50.0%	30.0%	30.0%
	80% to ≤125%	633	76.7%	40.0%	32.7%
	>125%	771	100.0%	36.4%	36.4%

Table III. *Correlation between the percentage of positive core and factors.*

	RDI group	Crude HR (95% CI)	*p*-Value	Adjusted HR* (95% CI)	*p*-Value
OS	<50%	Reference		Reference	
	50% to <80%	0.49 (0.26-0.91)	0.025*	0.39 (0.20-0.76)	**0.0055**
	80% to ≤125%	0.42 (0.25-0.71)	0.0013*	0.36 (0.20-0.63)	**0.0003**
	>125%	0.48 (0.23-0.99)	0.047*	0.30 (0.14-0.65)	**0.0023**
RFS	<50%	Reference		Reference	
	50% to <80%	0.71 (0.39-1.31)	0.28	0.74 (0.39-1.39)	0.35
	80% to ≤125%	0.51 (0.29-0.89)	0.018*	0.42 (0.23-0.77)	**0.0049**
	>125%	0.44 (0.20-1.01)	0.054	0.32 (0.14-0.74)	**0.0082**

*Adjusted for: Age, estimated glomerular filtration rate, residual tumor, final stage. Statistically significant *p*-values ($p<0.05$) are shown in bold.

chemotherapy (1). The JSAP-02 trial in Japan also demonstrated the efficacy of adjuvant chemotherapy with gemcitabine (9), and gemcitabine therapy has become the standard adjuvant chemotherapy for pancreatic cancer.

Clinical studies had been subsequently conducted to search for regimens more effective than gemcitabine therapy. The ESPAC-3 trial compared gemcitabine and 5-fluorouracil/folic acid, and showed that OS was similar with fewer adverse events occurring with gemcitabine (10). The following regimens were shown to be more effective than gemcitabine: S-1 in the JASPAC-01 trial conducted in Japan (2), gemcitabine plus capecitabine in the ESPAC-4 trial (11, 12), and modified FOLFIRINOX in the PRODIGE 24/CCTG PA.6 trial (12, 13). On the other hand, the APACT trial suggested that gemcitabine plus nab-paclitaxel may contribute to better OS than gemcitabine, but failed to demonstrate a higher efficacy for the primary endpoint of RFS (14).

Thus, there have been various studies to compare chemotherapy with chemoradiotherapy in adjuvant therapy, and to compare chemotherapy regimens in adjuvant therapy. On the other hand, there have been few studies to compare the duration of adjuvant chemotherapy. The duration of treatment was 6 months in the abovementioned randomized controlled trials of adjuvant chemotherapy.

There is another report that discussed the RDI of adjuvant chemotherapy for pancreatic cancer, as in this study. That article reported that RDI <72.3% and time interval from surgery to initiation of adjuvant chemotherapy of more than 51 days were independently associated with inferior OS, and concluded that early initiation and maintenance of RDI of S-1 monotherapy after pancreatectomy might improve the OS of patients with pancreatic ductal adenocarcinoma (15). However, no discussion was made regarding the duration of adjuvant chemotherapy.

At the ASCO 2020 Gastrointestinal Cancers Symposium, a phase II trial investigating the duration of adjuvant chemotherapy with S-1 for pancreatic cancer, the PACS-01 study (UMIN000012634), was reported. However, the percentage of patients who were unable to complete treatment was 35.3% at 6 months and 56.0% at 1 year, and there was no significant difference in RFS and OS between the 6-months and 1-year groups. It is possible that the RDI may not increase even if the duration of treatment is

extended to 1 year, and that simply extending the duration of treatment may not improve prognosis.

The present study was associated with some limitations, including its retrospective design and the relatively small number of cases. However, the results focus on the duration of adjuvant chemotherapy, which has rarely been investigated, and suggest that prolonged treatment may improve prognosis. In addition, prolonging the duration of treatment can be practiced at many facilities. This is of great significance in the treatment of pancreatic cancer, which is associated with a poor prognosis. Further studies, including a large-scale phase III randomized controlled trial are desirable.

Conclusion

In conclusion, the higher the RDI of S-1 in adjuvant chemotherapy, the better the OS and RFS. In adjuvant chemotherapy with S-1 for pancreatic cancer, a treatment period of 1 year may be preferable to 6 months.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

H.I. mainly acquired and analyzed the data, and wrote the draft. Y.F., I.N., K.T. and Y.K. participated in the data acquisition. E.H. supervised the research design and interpretation of the data and contributed to editing the article. All Authors participated in critical revision of the article for important intellectual content.

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