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ORIGINAL ARTICLE – PANCREATIC TUMORS

The Impact of Postoperative Complications on the Administration of Adjuvant Therapy Following Pancreaticoduodenectomy for Adenocarcinoma

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ABSTRACT

Background. The impact of postoperative complications on the administration of adjuvant therapy following pancreaticoduodenectomy (PD) for adenocarcinoma is still unclear.

Methods. A retrospective review of all patients undergoing PD at our institution between 1995 and 2011 was performed. Clinicopathological data, including Clavien–Dindo complication grade, time to adjuvant therapy (TTA), and survival, were analyzed.

Results. A total of 1,144 patients underwent PD for adenocarcinoma between 1995 and 2011. The overall complication rate was 49.1 % and clinically severe complications (≥IIIb) occurred in 4.2 %. Overall, 621 patients (54.3 %) were known to have received adjuvant therapy. The median TTA was 60 days. Although the presence of a complication was associated with a delay in TTA ($p = 0.002$), the grade of complication was not ($p = 0.112$). On multivariate analysis, only age > 68 years ($p < 0.001$) and length of stay >9 days ($p = 0.002$) correlated with no adjuvant therapy. Patients with postoperative complications were more likely to receive single adjuvant chemotherapy or radiation therapy (31.4 %) than were patients without complications (17.1 %; $p < 0.001$). Patients without a complication had a longer median survival compared with patients who experienced complications (19.5 vs. 16.1 months; $p = 0.001$). Patients without complications who received adjuvant therapy had longer median survival than patients with complications who received no adjuvant therapy (22.5 vs. 10.7 months; $p < 0.001$). Multivariate analysis demonstrated that complications [hazard ratio (HR) 1.16; $p = 0.023$] and adjuvant therapy (HR 0.67; $p < 0.001$) were related to survival.

Conclusion. Complications and no adjuvant therapy are common following PD for adenocarcinoma. Postoperative complications delay TTA and reduce the likelihood of multimodality adjuvant therapy. Identifying patients at increased risk for complications and those unlikely to receive adjuvant therapy warrants further investigation as they may benefit from a neoadjuvant approach.

Approximately 45,200 cases of pancreatic cancer (PC) are diagnosed yearly in the US, with 38,500-attributable cancer-related deaths.[1] The overall 5-year survival rate for PC is only 6 %,[1] and even for resectable cancers, the 5-year survival rate following pancreaticoduodenectomy (PD) is less than 20 %.[2–7] Local and systemic recurrence are common following PD, suggesting both systemic and local adjuvant therapy are necessary to improve outcomes.[8]

Several randomized studies of adjuvant treatment following pancreatic resection, including the European Study Group for Pancreatic Cancer 1 or 3 (ESPAC-1 or 3),[9,10] the Charite Onkologie 001 (CONKO-001),[11] and a prospective

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analysis at Johns Hopkins Hospital (JHH; Baltimore, MD, USA)[12] demonstrate a survival benefit with adjuvant therapy over surgery alone. Additionally, a retrospective analysis of 616 patients undergoing PD for PC who received postoperative adjuvant therapy demonstrated improved median survival (14 vs. 10 months) and 2-year survival (40 vs. 31 %) when compared with observation ($p = 0.003$).[4] Recently, a collaborative study demonstrated adjuvant therapy was associated with improved survival after PD.[5] Matched-pair analysis demonstrated overall survival (OS) was longer with adjuvant therapy (21.9 vs. 14.3 months median survival; $p < 0.001$).

Based on these results, adjuvant therapy is now considered standard treatment following PD for PC. Adjuvant chemotherapy (CT) typically commences within 8–10 weeks of surgical resection.[2–7] Several studies have demonstrated early initiation of adjuvant CT is associated with improved survival for colorectal[13–17] and breast cancers.[18–20] Murakami et al.[3] reported starting adjuvant CT within 20 days of pancreatic resection improves 5-year OS (52 vs. 26 %; $p = 0.013$) and 5-year disease-free survival (53 vs. 22 %; $p = 0.007$).

Postoperative complications are common following PD (30–50 %)[4,7,21–23] and we hypothesized that complications delay adjuvant therapy, resulting in adverse long-term outcomes. Postoperative complications appear to be associated with worse long-term outcomes in esophageal,[24,25] colorectal[26–28] and PCs.[4,22,29] However, the relationship of postoperative complications, time to initiation of adjuvant therapy and long-term survival for PC remains unclear, although some studies have started to explore this issue.[30,31]

This study analyzes the impact of postoperative complications on administration of adjuvant therapy and OS for a large cohort of patients undergoing PD for PC at our institution.

METHODS

Study Design and Participants

This study was approved by the Institutional Review Boards of JHH. We reviewed all patients who underwent PD for pancreatic adenocarcinoma at JHH between 24 January 1995 and 23 February 2011 (n = 1,443). We excluded patients who received neoadjuvant therapy (n = 114), initiated adjuvant therapy more than 6 months after surgery (n = 10), and those missing critical clinical information (n = 175). Clinical and pathologic data were obtained and confirmed by a chart review. Survival was determined by review of clinic notes, cancer center abstracting services, and the Social Security Death Index.

Surgical Procedures

Patients underwent either a pylorus-preserving PD, a classic PD, or a total pancreatectomy.[5] Surgical margins were considered positive if carcinoma was close (within 1 mm) or present at any of the final resection margins. Pathology specimens were reviewed by a single pathologist at JHH (RHH).[32]

Postoperative Complications

A more detailed report of our postoperative complications was described previously.[7] The present definition and clinical grading of postoperative pancreatic fistula (POPF) was according to the International Study Group (ISGPF) criteria.[33] All complications were categorized using the modified Clavien–Dindo classification,[34,35] which stratifies complications as grades 0–V. Complications of grade IIIb or more were regarded as severe. For patients with more than one complication, the highest grade was used for analysis.

Postoperative Adjuvant Therapy

Patients are routinely referred to a medical and radiation oncologist following PD for adenocarcinoma at JHH. Patients were encouraged to accept single-modality adjuvant CT, radiation therapy (RT), or both CT and RT.[4,21] CT regimens were either gemcitabine-based (alone or combined with paclitaxel) or 5-fluorouracil (FU) based (5-FU/leucovorin combined with oxaliplatin or irinotecan). For patients receiving RT, adjuvant external-beam RT was delivered with linear accelerators using multiple-field techniques, with the median RT dose of 50.4 Gy and daily fraction of 1.8 Gy.

Time to adjuvant therapy (TTA) was defined as the interval between the date of surgery and first adjuvant therapy treatment.

Statistical Analysis

Variables included in analyses were age, sex, length of stay (LOS), operative time, estimated blood loss (EBL), T stage, N stage, and complication grade. Categorical variables between groups were compared using the Chi-squared test or Fisher's exact test, of which factors found to be significant on univariate analysis were subjected to multivariate analysis using a logistic regression model. OS and TTA were analyzed as survival data. The survival curves were constructed using the Kaplan–Meier method,[36] and comparisons of OS or TTA between groups were made using the log-rank test or together with the Breslow test. OS (in months) with 95 % confidence intervals (CI) was

estimated within each group. The proportion of individuals surviving 2, 5, and 10 years was calculated using life tables. Factors found to be significant on univariate analysis were subjected to multivariate analysis using a Cox proportional hazards model.[37] All statistical analyses were performed using Statistical Package for the Social Sciences, version 16.0 (SPSS, Chicago, IL, USA).

RESULTS

Patient Demographics and Clinicopathological Characteristics

The 1,144 eligible patients included 600 (52.4 %) men and 544 (47.6 %) women, with a median age of 68 years (range 31–93 years). The median operative time was 380 min (range 230–792 min), with a median EBL of 700 ml (range 50–15,000 ml). Postoperative complications occurred in 562 patients (49.1 %), of which the leading three complication grades were II (n = 199, 17.4 %), IIIa (n = 171, 14.9 %) and I (n = 144, 12.6 %). 48 patients (4.2 %) experienced a severe complication (grade $\geq$ IIIb). 523 patients (45.7 %) received surgery alone, 472 (41.3 %) received multimodality adjuvant therapy, and 149 (13.0 %) received single-modality adjuvant CT (n = 126, 11.0 %) or RT (n = 23, 2.0 %). Among those patients who received CT (n = 598), 334 patients received single-agent CT, 186 patients received multi-agent CT, and 78 patients were unknown. Among 230 patients (38.5 %) receiving CT at JHH, seven patients did not finish CT due to toxicity or mortality, and eight patients switched CT regimen or agents for disease progression and metastasis. Of patients receiving RT (n = 495), 146 patients (29.5 %) received RT at JHH. The most common pathologic T stage was T3 (n = 819, 71.6 %), followed by T2 (n = 248, 21.7 %). Only 63 patients (5.5 %) underwent pancreatectomy with vascular resection and reconstruction. 912 patients (79.7 %) had lymph node metastasis, which included 788 with N1 (68.9 %) and 124 with N2 (10.8 %). LOS ranged from 4 to 374 days, with a median LOS of 9 days. 72 patients (6.3 %) had POPF, including 38 grade B (3.3 %) and 11 grade C (1.0 %) (Table 1).

TABLE 1 Patient demographics and clinicopathological factors (n = 1144)

	No. of patients	%
Age [years; median (range)]	68 (31–93)	
Sex		
Male	600	52.4
Female	544	47.6
Operative time [min; median (range)]	380 (230–792)	
EBL [ml; median (range)]	700 (50–15,000)	
Vessels resected		
No	1,081	94.5
PV, SMV, or IVC	60	5.2
HA, SMA, or MCA	3	0.3
POPF grade		
0	1,072	93.7
A	23	2.0
B	38	3.3
C	11	1.0
Complication grade		
0	582	50.9
I	144	12.6
II	199	17.4
IIIa	171	14.9
IIIb	23	2.0
IVa	13	1.1
IVb	4	0.4
V	8	0.7
LOS [days; median (range)]	9 (4–374)	
Adjuvant therapy		
None	523	45.7
CT + RT	472	41.3
CT	126	11.0
RT	23	2.0
T stage		
pT1	43	3.7
pT2	248	21.7
pT3	819	71.6
pT4	34	3.0
N stage		
pN0	232	20.3
pN1	788	68.9
pN2	124	10.8

EBL estimated blood loss, *PV* portal vein, *SMV* superior mesenteric vein, *IVC* inferior vena cava, *HA* hepatic artery, *SMA* superior mesenteric artery, *MCA* middle colic artery, *POPF* postoperative pancreatic fistula, *LOS* length of stay, *CT* chemotherapy, *RT* radiation therapy

Comparison of Clinicopathological Factors According to Adjuvant Therapy

Of the 1,144 patients, only 621 (54.3 %) received adjuvant therapy, and 523 (45.7 %) received none. Clinicopathological characteristics of the two groups are shown in Table 2. There were no significant differences in sex, operative time, EBL, postoperative complication rate, T stage, or N stage between the two groups. However, age > 68 years [odds ratio (OR) 0.457; $p < 0.001$] and LOS > 9 days (OR 0.685; $p = 0.002$) was associated with a decreased likelihood of receiving adjuvant therapy. Multivariate analysis using a linear regression model demonstrated that both age > 68 years and

TABLE 2 Comparison of clinicopathological factors according to adjuvant therapy and postoperative complication n after PD for pancreatic head cancers (n = 1,144)

	Adjuvant therapy							Postoperative complication						
	No (n = 523)	Yes (n = 621)	p-value[a]	OR[b]	OR[b] (95 % CI)		p-value[b]	No (n = 582)	Yes (n = 562)	p-value[a]	OR[b]	OR[b] (95 % CI)		p-value[b]
					Lower	Upper						Lower	Upper	
Age (years)			<0.001							0.003				
≤68	214	374						324	264		0.639	0.503	0.813	<0.001
>68	309	247		0.47	0.371	0.597	<0.001	258	298					
Sex			0.324							0.008				
Male	266	334						283	317		1.326	1.045	1.684	0.02
Female	257	287						299	245					
Operative time (min)			0.053							<0.001				
≤380	286	304						335	255		0.582	0.457	0.74	<0.001
>380	237	317						247	307					
EBL (ml)			0.169							0.098				
≤700	274	300						306	268					
>700	249	321						276	294					
LOS (days)			0.002							0.000[a]				
≤9	243	347						428	162					
>9	280	274		0.733	0.577	0.933	0.011	154	400					
T stage			0.103							0.017	0.706	0.572	0.872	0.001
pT1	21	22						29	14					
pT2	130	118						138	110					
pT3	357	462						402	417					
pT4	15	19						13	21					
N stage			0.561							0.056				
pN0	110	122						131	101					
pN1, pN2	413	499						451	461					
Postoperative														

[a] Univariate analysis of categorical variables between the two groups was performed using the Chi-squared test

[b] Significant factors were then subjected to multivariate analysis using a logistic regression model

PD pancreaticoduodenectomy, *EBL* estimated blood loss, *LOS* length of stay, *CI* confidence interval, *OR* odds ratio
complication0.471 No260322 Yes263299[a] Univariate analysis of categorical variables between the two groups was performed using the Chi-squared test

[b] Significant factors were then subjected to multivariate analysis using a logistic regression model

LOS > 9 days were associated with a decreased chance of receiving adjuvant therapy.

Comparison of Clinicopathological Factors According to Postoperative Complication

Postoperative complications occurred in 562 (49.1 %) patients. Clinicopathological characteristics stratified according to postoperative complications are shown in Table 2. There were no significant differences in EBL and N stage between the patients with and without postoperative complications. On univariate analysis, factors associated with postoperative complications included higher T stage ($p = 0.017$), male sex (OR 1.367; $p < 0.001$), age > 68 - years (OR 1.418; $p < 0.001$), operative time > 380 min (OR 1.633; $p < 0.001$), and LOS > 9 days ($p = 0.002$). Multivariate analysis revealed male sex, age > 68 years, operative time > 380 min, and T stage were each independent predictors of postoperative complications after PD for PC (Table 2).

Association between Postoperative Complications and Adjuvant Therapy Receipt

Postoperative complications occurred in 49.1 % of patients, of which one-eighth were severe complications (grade ≥IIIb). Complication grade (0–V), postoperative

TABLE 3 Association between postoperative complication and adjuvant therapy in patients undergoing PD for pancreatic head cancers

	Adjuvant therapy (n = 1,144)		p-value	Adjuvant therapy modality (n = 621)		p-value
	No (n = 523)	Yes (n = 621)		CT + RT (n = 472)	CT or RT (n = 149)	
Complication grade			0.001			0.001
0	260	322		267	55	
I	61	83		58	25	
II	81	118		80	38	
IIIa	84	87		60	27	
IIIb	16	7		6	1	
IVa	10	3		1	2	
IVb	3	1		0	1	
V	8	0				
Postoperative complication			0.471			<0.001
No	260	322		267	55	
Yes	263	299		205	94	
Severe complication (≥IIIb)			<0.001			0.332
No	486	610		465	145	
Yes	37	11		7	4	

Categorical variables between the two groups were compared using the Chi-squared test or Fisher's exact test

PD pancreaticoduodenectomy, *CT* chemotherapy, *RT* radiation therapy

complication (yes or no) and severe complications (≥IIIb) were compared (Table 3). There was no relationship between the occurrence of any complication and administration of adjuvant therapy. However, higher-grade complications ($p = 0.001$) and severe complications ($p < 0.001$) were significantly associated with not receiving adjuvant therapy. In a subgroup of patients receiving adjuvant therapy, associations between the presence of a postoperative complication, grade of postoperative complication, severe complication, and adjuvant therapy modality were also investigated. Single-modality CT or RT was associated with both the presence ($p < 0.001$) and grade ($p = 0.001$) of postoperative complication. More patients with postoperative complications received single-modality CT or RT (31.4 %) than patients without complications (17.1 %; $p < 0.001$).

Comparison of Clinicopathological Factors According to Time to Adjuvant Therapy

The overall median TTA for the 621 patients who received adjuvant therapy was 60 days. TTA survival curves were constructed using the Kaplan–Meier method,[36] and univariate analysis of TTA between groups were made using the Breslow test. The presence of a postoperative complication significantly delayed the median TTA ($p = 0.002$). All other factors, including complication grade and severe complications (≥IIIb), did not correlate with TTA.

Survival and Prognostic Factors

The estimated OS rates of all 1,144 patients undergoing PD for PC were 37.2 % at 2 years, 14.8 % at 5 years, and 10.2 % at 10 years. Median OS was 18.1 months (95 % CI 16.9–19.4 months). The prognostic impact of complications and adjuvant therapy were investigated by evaluating clinicopathological factors associated with OS using univariate analyses and multivariate analyses (Table 4).

Univariate analysis showed that sex ($p = 0.486$) and LOS ($p = 0.196$) were not associated with OS. There were nine prognostic factors significantly correlated with OS: age ($p < 0.001$), operative time ($p < 0.001$), EBL ($p = 0.010$), T stage ($p < 0.001$), N stage ($p < 0.001$), complication grade ($p < 0.001$), any complication ($p = 0.001$), severe complication (≥IIIb) ($p < 0.001$), and adjuvant therapy ($p < 0.001$). We chose presence of a complication to perform multivariate analysis using a Cox proportional hazards model, together with the other six factors. In a subgroup analysis of 621 patients receiving adjuvant therapy, TTA was not associated with OS ($p = 0.137$), but receipt of multimodality adjuvant therapy correlated to longer median OS (21.7 vs. 19.2 months; $p = 0.037$).

Multivariate analysis showed seven factors remained independently associated with OS: N stage (HR 1.67; $p < 0.001$), age (HR 1.39; $p < 0.001$), operative time (HR 1.36; $p < 0.001$), T stage (HR 1.19; $p = 0.004$), EBL (HR 1.17; $p = 0.019$), complication (HR 1.16; $p = 0.023$), and

TABLE 4 Univariate and multivariate analysis of OS of patients undergoing PD for pancreatic head cancers (n = 1,144)

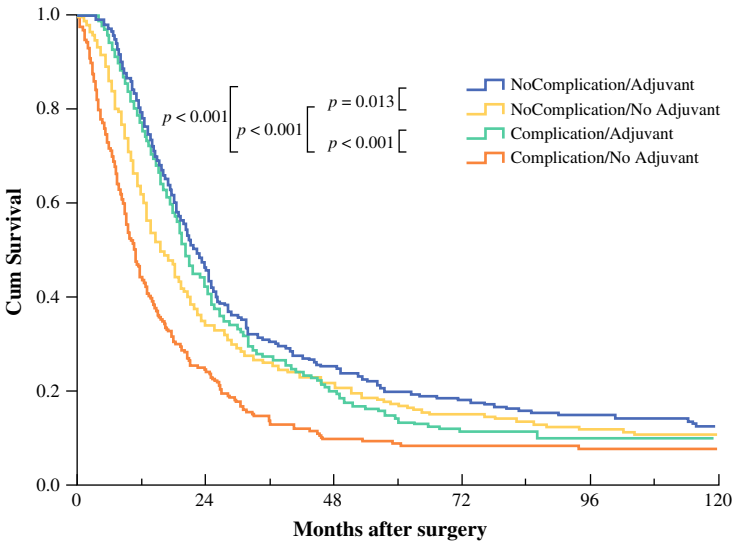
	No. of patients	%	OS (%)		OS (months) (Univariate analysis)				Multivariate analysis			
					Median	95 % CI		p-value	HR	HR (95 % CI)		p-value
			2-year	5-year		Lower	Upper			Lower	Upper	
Overall	1,144	100	37.2	14.8	18.133	16.912	19.355					
Age (years)								<0.001	1.391	1.222	1.583	<0.001
≤68	588	51.4	42.1	17.7	20.333	18.565	22.101					
>68	556	48.6	32.1	11.9	15.3	13.57	17.03					
Sex								0.486				
Male	600	52.4	36.9	15.4	18.233	16.041	20.026					
Female	544	47.6	37.5	14.2	18.033	16.041	20.026					
Operative time (min)								<0.001	1.356	1.192	1.544	<0.001
≤380	590	51.6	42.6	18.6	19.533	17.757	21.31					
>380	554	48.4	31.4	10.7	15.967	14.426	17.507					
EBL (ml)								0.01	1.166	1.025	1.327	0.019
≤700	574	50.2	41.0	16.6	19.533	17.738	21.329					
>700	570	49.8	33.5	13.1	17	15.653	18.347					
LOS (days)								0.196				
≤9	590	51.6	39.5	14.6	19.2	17.752	20.648					
>9	554	48.4	34.8	15	16.433	14.834	18.033					
T stage								<0.001	1.194	1.058	1.348	0.004
pT1	43	3.8	67.5	35.9	46.167	14.253	78.08					
pT2	248	21.7	39.7	17.7	19.4	16.525	22.275					
pT3	819	71.6	35.7	13	17.8	16.499	19.101					
pT4	34	3	19.9	13.3	10.667	8.286	13.048					
N stage								<0.001	1.666	1.408	1.971	<0.001
pN0	232	20.3	53.9	27.5	26.467	20.836	32.097					
pN1, pN2	912	79.7	33	11.7	16.633	15.487	17.779					
Complication grade								<0.001				
0	582	50.9	40.6	18.4	19.533	17.911	21.156					
I	144	12.6	34.1	8.2	16.8	12.067	21.533					
II	199	17.4	39	12.2	19.1	17.125	21.075					
IIIa	171	14.9	30.4	13.3	14.533	12.522	16.545					
IIIb	23	2	32.7	13	11.967	4.735	19.198					
IVa	13	1.1	20.7	0	15.1	0	30.64					
IVb	4	0.3	0	0	2.967	0	7.54					
V	8	0.7	0	0	0.433	0	1.45					
Postoperative complication								0.001	1.159	1.021	1.316	0.023
No	582	50.9	40.6	18.4	19.533	17.911	21.156					
Yes	562	49.1	33.6	11	16.133	14.518	17.749					
Severe complication (≥IIIb)								<0.001				
No	1,096	95.8	37.9	15.2	18.367	17.16	19.573					
Yes	48	4.2	21.1	6.4	7.433	2.12	12.747					
Adjuvant therapy								<0.001	0.673	0.592	0.765	<0.001
No	523	45.7	28.9	12.5	13	11.647	14.353					
Yes	621	54.3	44.2	16.7	20.967	19.278	22.656					
Adjuvant therapy modality[a]								0.037				
CT + RT	472	41.3	45.7	17.6	21.667	19.608	23.726					
CT or RT	149	13	39.6	13.9	19.2	16.804	21.596					

TABLE 4 continued

	No. of patients	%	OS (%)		OS (months) (Univariate analysis)				Multivariate analysis			
					Median	95 % CI		*p*-value	HR	HR (95 % CI)		*p*-value
			2-year	5-year		Lower	Upper			Lower	Upper	
TTA (days)[a]								0.137				
≤60	312	27.3	44.8	19.6	20.967	18.706	23.228					
>60	309	27	43.6	14.5	20.6	17.987	23.213					

PD pancreaticoduodenectomy, *OS* overall survival, *HR* hazard ratio, EBL estimated blood loss, *LOS* length of stay, *CT* chemotherapy, *RT* radiation therapy, *TTA* time to adjuvant therapy, *CI* confidence interval

[a] Analyzed in a subgroup of 621 patients receiving adjuvant therapy after PD for pancreatic head cancers



No. at Risk

NoComplication/Adjuvant	319.5	139.0	62.5	39.0	29.0	19.5
NoComplication/No Adjuvant	257.5	83.5	47.5	33.5	19.5	14.0
Complication/Adjuvant	296.0	109.5	42.5	19.0	10.5	7.5
Complication/No Adjuvant	260.0	55.0	19.0	14.5	12.0	8.5

FIG. 1 Survival curves of patients who received adjuvant therapy with or without complications and those who received no adjuvant therapy with or without complications after pancreaticoduodenectomy for pancreatic head cancers (Kaplan–Meier method)

adjuvant therapy (HR 0.67; $p < 0.001$). Patients without a complication had a longer median OS (19.5 vs. 16.1 months; $p = 0.001$) and patients who received no adjuvant therapy had a shorter median OS (13.0 vs. 21.0 months; $p < 0.001$).

Nevertheless, patients without complications who received adjuvant therapy had longer survival compared with patients who did not receive adjuvant therapy (22.5 vs. 15.7 months; $p = 0.013$), and compared with patients who experienced a complication and received no adjuvant therapy (22.5 vs. 10.7 months; $p < 0.001$). Patients with complications who received no adjuvant therapy had shorter survival than those who received adjuvant therapy (10.7 vs. 20.4 months; $p < 0.001$), and those without complications who received no adjuvant therapy (10.7 vs. 15.7 months; $p < 0.001$) (Fig.1).

DISCUSSION

Receiving adjuvant therapy is associated with improved survival and is typically recommended after resection of PC.[4,5,9–12,38] Early initiation of adjuvant CT appears to have a survival benefit for some cancer types.[13–20] including PC.[3] Postoperative complications have been associated with worse long-term outcomes in esophageal cancer,[24,25] colorectal cancer,[26–28] and PC.[4,22,29] However, the relationship between postoperative complications following PD for PC and receipt of adjuvant therapy is unclear.

In this large cohort of patients following PD, only 54.3 % of patients received adjuvant therapy. The large proportion of patients (45.7 %) who do not receive adjuvant CT is similar to other reports.[4,22,29] Lima et al.[17]

suggested that slow recovery from surgery and postsurgical complications might influence whether a patient receives adjuvant therapy following colorectal resections.

We attempted to identify reasons for patients not receiving adjuvant therapy. Univariate and multivariate analysis found age > 68 years ($p < 0.001$) and LOS > 9 days ($p = 0.002$) were associated with a lower likelihood of receiving adjuvant therapy, suggesting that old age and slow recovery were major obstacles. Since age ≥ 75 years was found to be a risk factor for early mortality following PD,[39] it is also possible that adjuvant recommendations were less aggressive for elderly patients.

Interestingly, although the presence of a complication correlated with delays in TTA, the grade and severity of complication did not. However, the Clavien–Dindo grade of complication ($p = 0.001$), and particularly more severe complications (≥IIIb) ($p < 0.001$), significantly correlated to no adjuvant therapy being administered. Additionally, even when patients with postoperative complications did receive adjuvant therapy, single-modality adjuvant therapy ($p = 0.001$) was more frequently chosen. This is important because no adjuvant therapy and use of CT or RT alone correlated with worse OS.

The overall median TTA in the 621 patients who received adjuvant therapy was 60 days, which is somewhat longer than we expected. In comparison, the median TTA was 46 days for CT and 61 days for CRT in the ESPAC-1 trial,[9] 36 days in the CONKO-001 trial,[11] and 55 days in the ESPAC-3 trial.[10] It is possible that the nature of these protocol-driven randomized trials impacted the TTA compared with our retrospective review.

Several studies have investigated the impact of postoperative complications on long-term survival in PC,[3,4,22,29] but only two have focused on TTA.[3,29] Murakami et al.[3] reported median TTA for 104 patients was only 20 days and only postoperative complications related to longer TTA. However, this study only included patients who actually received adjuvant therapy and TTA was categorized as ≤20 days or >20 days. Petermann et al.[29] reported delayed TTA for patients with severe postoperative complications from PD (82 vs. 55 days), but grade V complications were excluded, only 96 patients were evaluated, and less than half actually received adjuvant therapy.

We evaluated detailed TTA data and compared TTA amongst groups based on clinicopathological factors. Postoperative complications significantly delayed median TTA (62 vs. 55 days; $p = 0.002$), but 7 days is of questionable clinical significance. For patients receiving adjuvant therapy, TTA was not associated with improved survival. Interestingly, neither complication grade nor severe complications (≥IIIb) correlated with TTA, possibly due to the small number of grade IV and V complications.

Similar to other studies,[3,4,22] we demonstrated that patients without a complication had a longer OS (19.5 vs. 16.1 months; $p < 0.001$), particularly for patients who received no adjuvant therapy (15.7 vs. 10.7 months; $p < 0.001$). The impact of postoperative complications on survival was not statistically significant for patients who received adjuvant therapy (20.4 vs. 22.5 months; $p > 0.05$). On the other hand, patients who received no adjuvant therapy had a significantly worse survival regardless of whether they had a complication ($p < 0.001$) or not ($p = 0.013$).

CONCLUSIONS

Complications and no administration of adjuvant therapy are common (49.1 % and 45.7 %, respectively) following PD for PC. Although the presence of complications does not appear to impact whether adjuvant therapy is administered, the TTA is longer and use of single-modality adjuvant therapy is more common. Higher-grade complications result in significantly higher rates of no adjuvant therapy administration. Complications and lack of multimodality adjuvant therapy correlate to worse OS following PD for PC. Identifying patients at increased risk for complications and those unlikely to receive CRT warrants further investigation as they may benefit from a neoadjuvant approach.

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