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Prognostic Impact of Unplanned Total Pancreatectomy in Pancreatic Ductal Adenocarcinoma: A Retrospective Analysis

Dongha Lee¹  | Keiko Kamei¹ | Chihoko Nobori¹ | Yuta Yoshida¹ | Takaaki Murase¹ | Atsushi Takebe¹ | Takuya Nakai¹ | Mamoru Takenaka²  | Takaaki Chikugo³ | Ippei Matsumoto¹ 

¹Department of Surgery, Kindai University Faculty of Medicine, Osakasayama, Japan | ²Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osakasayama, Japan | ³Department of Pathology, Kindai University Faculty of Medicine, Osakasayama, Japan

Correspondence: Ippei Matsumoto (ippeimm@gmail.com)

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ABSTRACT

Background: This study evaluated the clinical significance of an unplanned total pancreatectomy (TP) by comparing surgical outcomes of planned and unplanned TP for pancreatic ductal adenocarcinoma (PDAC).

Methods: Forty-two patients who underwent TP for PDAC between 2009 and 2020 at the Kindai University Hospital were retrospectively analyzed. We evaluated the differences in the prognosis and related factors between planned and unplanned TP, and independent prognostic factors of TP for PDAC.

Results: Twenty-three patients underwent planned TP, and 19 underwent unplanned TP. There were no significant differences in clinicopathological data between the two groups, except for microscopic vascular invasion. However, the unplanned TP group had significantly better overall survival (OS) and recurrence-free survival (RFS) times than the planned TP group. In the multivariate analysis of the prognostic factors of TP for PDAC, a planned TP and not receiving or completing postoperative adjuvant chemotherapy (AC) were independent poor prognostic factors.

Conclusion: This study supports a rigorous approach to margin clearance in TP for PDAC to achieve curative negative margins in cancer-positive pancreatic resection stumps. However, the prognosis of a planned TP for PDAC is extremely poor, and adequate preoperative and multidisciplinary treatment may be necessary to prolong the prognosis.

1 | Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most progressive and fatal malignancies. PDAC remains the third leading cause of cancer-related deaths in the United States in 2024, with a 5-year survival rate of 13% [1]. Complete surgical resection can cure localized PDAC. Among the surgical procedures for PDAC, pancreaticoduodenectomy (PD), distal pancreatectomy (DP), and total pancreatectomy (TP) are widely performed depending on the tumor's location and behavior.

TP has traditionally been performed for the following reasons: achieving complete tumor clearance; avoiding pancreatic anastomosis-related complications; residual pancreatectomy for residual cancer; rescue pancreatectomy after a leaking pancreaticogastrostomy or pancreatojejunostomy with sepsis or bleeding [2]. Compared with organ-preserving pancreatectomies such as PD or DP, TP causes a complete loss of pancreatic exocrine and endocrine functions, which leads to a decreased quality of life (QOL). Previous studies until the 20th century showed that TP for PDAC may be associated with higher operative morbidity

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and poorer prognosis than PD [3–5]. However, recent studies in the 2000s showed that survival outcomes in PDAC may be equivalent between TP and PD, with recent advances in surgical techniques and perioperative management such as insulin therapy and pancreatic enzyme replacement therapy [2, 6–9].

Curative negative margin (R0) resection is considered the only chance to survive PDAC and is the most important factor determining the prognostic outcome [10, 11]. In general, TP is planned for patients with PDAC with massively extended tumors, multiple lesions of the pancreas, or residual tumors after PD or DP. However, positive margins of the transected pancreas, as established by the intraoperative examination of frozen sections, are occasionally encountered during pancreatectomy for PDAC, even though careful preoperative and intraoperative evaluations are performed. The rate of occurrence of positive margins during pancreatectomy is reportedly between 11% and 21.7% during pancreatectomy [12–14]. Positive margins in PDAC after surgical resection are an independent negative predictor of long-term survival [11, 15]. Therefore, extending pancreatic resection to a negative resection stump for a cancer-positive intraoperative frozen section (IFS) analysis has become popular among pancreatic surgeons. However, the survival benefit of additional pancreatic resection due to cancer-positive pancreatic resection margins in PDAC remains debatable. Studies have shown a prognostic benefit of converting a positive pancreatic resection margin to a negative margin with additional pancreatic resection [14, 16, 17], while others have not [13, 18, 19]. Moreover, the clinical significance of TP in achieving negative pancreatic margins (unplanned TP) has not been thoroughly investigated.

This study aimed to clarify the prognostic impact of an unplanned TP for PDAC by comparing the surgical outcomes between planned and unplanned TP and analyzing the prognostic factors of TP.

2 | Methods

2.1 | Patient Selection and Study Design

This retrospective single-center study included 45 consecutive patients who underwent TP for PDAC between April 2009 and December 2020. Three patients were excluded for the following reasons: one patient had a macroscopically positive margin (R2) following TP; one had double cancer (PDAC and bile duct cancer); one had severe acute pancreatitis, and curative surgery was postponed for a long time regardless of tumor progression. Finally, 42 patients who underwent complete macroscopic (R0/R1) resection TP for PDAC were included.

Clinical data included age, sex, body mass index, preoperative diabetes mellitus, preoperative bile drainage, neoadjuvant chemotherapy, adjuvant chemotherapy (AC), serum carbohydrate antigen 19-9 (CA19-9) level at the time of diagnosis, preoperative albumin level, glycated hemoglobin level, postoperative albumin level (1–2 months after surgery), tumor location and size, resectability status defined by the National Comprehensive Cancer Network (NCCN) guidelines [20], intraoperative data, postoperative complications, pathological data such as the T and N status according to the seventh American Joint Committee on

Cancer/Union for International Cancer Control TNM classification [21], and survival outcomes.

All patients who underwent TP were grouped based on whether the surgery was planned ($n=23$) or unplanned ($n=19$). A planned TP was defined as TP originally intended based on preoperative imaging findings such as tumor location and vascular invasion. An unplanned TP was defined as unintentional TP owing to cancer-positive pancreatic resection margins or other intraoperative findings when the reconstruction of the pancreatogastrointestinal anastomosis was impossible in cases of PD or when additional pancreatic resection was impossible because the gastroduodenal artery and/or the bile duct could not be preserved in cases of DP. The resectability status of PDAC and the operative procedure were decided at a joint conference among gastroenterologists, hepato-biliary-pancreatic surgeons, and oncologists.

Surgical outcomes were compared between the planned and unplanned TP groups. The prognostic factors of TP for PDAC were also evaluated. All patients provided written informed consent before surgery according to the rules and regulations of our institution. This study was approved by the Ethics Committee of Kindai University Faculty of Medicine (approval number: R04-164) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent for participation was not required because of the retrospective nature of the study.

2.2 | Postoperative Complications and Their Definitions

Postoperative complications were evaluated using a modified Clavien–Dindo classification [22]. Complications of grade $\geq$ III were regarded as clinically significant events compared with severe complications. Delayed gastric emptying was evaluated according to the International Study Group of Pancreatic Surgery grading classification [23].

2.3 | Postoperative AC and Management

Patients were eligible for AC if they underwent R0/R1 resection for PDAC with histological confirmation. Prior to AC, patients had to fully recover from surgery, with an Eastern Cooperative Oncology Group performance status of ≤ 2 . After postoperative wound healing, AC was administered as soon as possible. The criteria for gemcitabine AC administration (dose, continuation, and discontinuation) were in accordance with those of the CONCO-001 trial [24]. Patients received six cycles of gemcitabine every 4 weeks, consisting of 3 weekly infusions of gemcitabine (1000 mg/m^2), followed by a 1-week break. The criteria for S-1 AC administration (dose, continuation, and discontinuation) were in accordance with those of the JASPAC-01 trial [25]. The S-1 AC regimen involved the administration of 80–120 mg of S-1 (according to body surface area) twice a day for 4 weeks; this was repeated every 6 weeks for four courses. Treatment was discontinued when recurrence occurred during AC, or uncontrollable adverse reactions did not resolve following dose modification and/or temporary drug withdrawal.

2.4 | Follow-Up Management and Survival

Follow-up data were collected until March 31, 2023. Computed tomography (CT) was used to screen for recurrence at 3-month intervals postoperatively. When recurrence was suspected, magnetic resonance imaging and/or ^{18}F -fluorodeoxyglucose positron emission tomography was performed as required. Recurrent disease was defined as recurrent lesions detected on imaging and was not diagnosed solely based on elevated levels of tumor markers. Survival and time to recurrence were recorded for each patient. Overall survival (OS) was defined as the time from the date of surgery or neoadjuvant treatment to death, cancer-related death, or the last follow-up date. Recurrence-free survival (RFS) was calculated from the date of surgery to recurrence.

2.5 | Pathological Evaluation of Cancer-Positive Pancreatic Resection Margins and Prognosis

Based on the pathological findings, cancer-positive pancreatic resection margins during surgery were classified into three patterns: high-grade PanIN, stromal invasion, and mixed (both high-grade PanIN and stromal invasion types). Prognosis was examined in patients with cancer-positive pancreatic resection margins according to the classification.

2.6 | Statistical Analysis

The data were analyzed using JMP statistical software (version 16; SAS Institute, Japan). OS and RFS rates were calculated using the Kaplan–Meier method, and differences in survival rates between the two groups were compared using the Cox hazard test. Multivariate analysis was performed using clinically relevant variables, including age and tumor burden; the chosen variables were included regardless of their significance as determined through the univariate analysis. This approach minimizes potential biases arising from variable selection based solely on p -values. Multivariate analysis was performed using the Cox proportional hazards regression model. Pearson's chi-square test was used to compare categorical variables. A p -value of <0.05 was considered statistically significant.

3 | Results

3.1 | Clinicopathological Data of All Patients

Overall, 42 patients who underwent TP were included in this study. Planned and unplanned TPs were performed on 23 and 19 patients, respectively. The reasons for a planned TP were as follows: residual cancer in nine patients, PDAC located from the head to the neck of the pancreas (Phb or Pbh) in nine, multiple tumors in four, and PDAC with walled-off necrosis due to severe acute pancreatitis in one. The reasons for an unplanned TP were as follows: cancer-positive pancreatic resection margins in 17 patients based on IFS analysis in 14 patients, permanent pathological analysis in three patients, tumor invasion of the gastroduodenal artery in one patient with a

planned DP, and PDAC diagnosed on the pathological specimen after Frey's operation in one patient (none of the tumors were detected on CT images). Among the 17 patients with cancer-positive pancreatic resection margins, 13 underwent conversion from a planned PD to TP, and four underwent conversion from a planned DP to TP. Figure 1 shows a representative preoperative CT image of these patients. Among patients with cancer-positive pancreatic resection margins based on IFS analysis during pancreatectomy, additional pancreatic resections were performed for a median of 2.0 times (range: 0–3 times) in a planned PD and for a median of 2.0 times (range: 0–2 times) in a planned DP. The other baseline characteristics of the patients are presented in Table 1. Overall, 10 patients required curative resection of other organs (common hepatic artery resection [$n=2$], partial gastrectomy [$n=6$], and partial colectomy [$n=2$]). The rate of R0 resection was 81%. The rate of severe postoperative complications (Clavien–Dindo classification, grade IIIa or higher) was 14%. The rates of AC initiation and completion were 45% and 36%, respectively. Among the 19 patients who initiated AC, two and 17 received gemcitabine and S-1, respectively. Fifteen patients completed AC (gemcitabine [$n=1$] and S-1 [$n=14$]), whereas 27 did not receive or complete AC; these patients did not complete AC for the following reasons: poor physical condition [$n=13$], early recurrence [$n=9$], perioperative death [$n=1$], unknown data [$n=3$], and refusal [$n=1$].

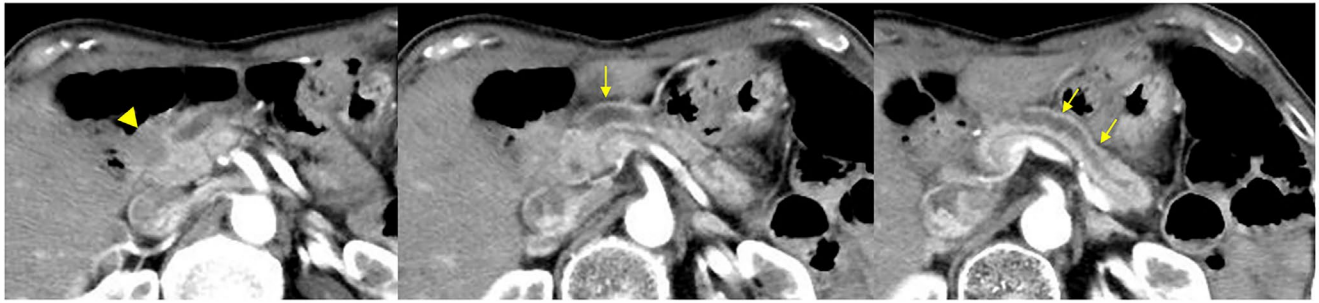
3.2 | OS and RFS of All Patients

The median follow-up time was 20 months (range: 1–108 months). The perioperative mortality rate was 2%. By the last follow-up visit, 36 patients had died. Overall, 27 patients died from the primary disease and nine from other diseases (pneumonia [$n=2$], unspecified sudden death without recurrence [$n=2$], lung cancer [$n=1$], ovarian cancer [$n=1$], postoperative hemorrhage [$n=1$], liver abscess [$n=1$], and hypertrophic cardiomyopathy [$n=1$]). The median OS time (MST) and disease-specific survival time after initial treatment were 20 and 26 months, respectively. The 1-, 3-, and 5-year OS rates were 59%, 24%, and 17%, respectively. The 1-, 3-, and 5-year disease-specific survival rates were 66%, 31%, and 22%, respectively. The MST after surgery was 20 months, and the 1-, 3-, and 5-year OS rates were 59%, 24%, and 17%, respectively. Disease recurrence after TP was identified in 31 patients with liver metastasis ($n=11$), peritoneal dissemination ($n=8$), locoregional recurrence ($n=8$), lung metastasis ($n=3$), and distant lymph node metastasis ($n=3$). The median RFS time (mRFS time) was 11 months. The RFS rates at 1, 3, and 5 years were 43%, 20%, and 16%, respectively.

3.3 | Planned Versus Unplanned TP

There were no significant differences in patient characteristics, operative data, pathological results, or short-term postoperative outcomes between the groups (Table 1). However, the unplanned TP group had a significantly better OS (MST: 34 vs. 12 months, $p=0.009$) and disease-specific survival (median disease-specific time: 44 vs. 14 months, $p=0.005$) after initial treatment than the planned TP group. OS after surgery

a)



b)

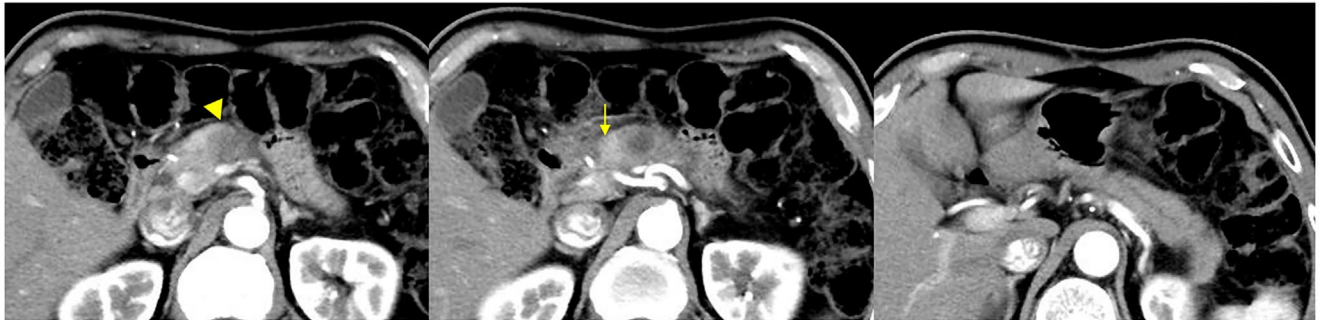


FIGURE 1 | Representative preoperative CT scans in patients with unplanned TP due to cancer positive pancreatic margin. Seventeen patients required unplanned TP. (a) CT showing a hypo-enhanced tumor in the pancreatic head (arrowhead). Due to cancer positive pancreatic resection stump based on intraoperative frozen section (IFS) analysis, additional pancreatic resection was performed three times for PD (arrow). (b) CT showing a hypo-enhanced tumor in the pancreatic body (arrowhead). Due to cancer positive pancreatic resection stump based on IFS analysis (arrow), TP was performed.

was also significantly better in the unplanned TP group (MST: 32 vs. 12 months, $p=0.007$). Additionally, the unplanned TP group had a significantly better RFS than the planned TP group (mRFS time: 21 vs. 7 months, $p=0.003$; Figure 2). Disease recurrence was observed in 20 patients who underwent planned TP. The initial recurrence sites were as follows: liver metastasis ($n=9$), peritoneal dissemination ($n=5$), locoregional recurrence ($n=5$), lung metastasis ($n=2$), and distant lymph node metastasis ($n=2$). In contrast, 11 patients who underwent unplanned TP experienced disease recurrence. The initial recurrence sites included liver metastasis ($n=2$), peritoneal dissemination ($n=3$), locoregional recurrence ($n=3$), lung metastasis ($n=1$), and distant lymph node metastasis ($n=1$). There was no significant difference in the distribution of initial recurrence sites between the groups ($p=0.595$).

3.4 | Prognostic Factors

Table 2 presents the prognostic factors of TP for PDAC. A planned TP, high serum CA19-9 levels at diagnosis ($>37\text{IU/mL}$), lymph node metastases, and not receiving or completing AC were identified as poor prognostic factors on univariate analysis. Multivariate analysis revealed that a planned TP ($p=0.035$; hazard ratio [HR]: 2.52; 95% confidence interval [CI]: 1.07–5.94) and not receiving or completing AC ($p=0.003$;

HR: 3.74; 95% CI: 1.58–8.82) were independent poor prognostic factors for OS.

3.5 | Completion Versus No or Incompletion of AC

We found that patients who did not receive or complete AC had a significantly worse prognosis than those who completed AC (MST after initial treatment: 12 vs. 36 months, $p=0.004$; after surgery: 11 vs. 36 months, $p<0.001$, respectively, Figure S1). Failure to initiate or complete AC was significantly more frequent in patients who underwent simultaneous resection of other organs ($p=0.007$; Table S1). None of the patients who underwent TP with a complicated resection of other organs completed postoperative AC. There were no significant differences in other clinicopathological factors between patients who completed AC and those who did not receive or complete AC.

3.6 | Relationship Between Pathological Types of Cancer-Positive Pancreatic Resection Margins and Survival Outcomes

Among the 17 patients with cancer-positive pancreatic resection margins who required an unplanned TP, 13 for whom microscopic evaluation was available were analyzed. Based on the

TABLE 1 | Clinicopathological data of planned TP and unplanned TP groups.

Factors	Total (n = 42)	Planned TP group (n = 23)	Unplanned TP group (n = 19)	p
Age (year), median (range)	69 (47–87)	68 (47–85)	71 (55–87)	0.323
Sex (male), n (%)	28 (67)	15 (65)	13 (68)	0.827
Preoperative body mass index, median (range)	21 (15–32)	22 (15–32)	20 (16–27)	0.658
Preoperative diabetes melitus, n (%)	26 (62)	14 (61)	12 (63)	0.879
Preoperative biliary drainage, n (%)	11 (26)	4 (17)	7 (37)	0.154
Main tumor location, Ph/Pb/Pt	23/12/7	11/9/3	12/3/4	0.243
Tumor size of preoperative image (mm), median (range)	22 (8–42)	22 (8–38)	20 (10–42)	0.437
Resectability status, R/BR/UR, n	24/16/2	13/9/1	11/7/1	0.982
Preoperative chemotherapy, n (%)	13 (31)	6 (26)	7 (37)	0.453
Serum CA19–9 levels at diagnosis (U/mL), median (range)	66 (3–2953)	62 (3–2953)	82 (3–946)	0.723
Preoperative albumin levels (g/dL), median (range)	4 (2.1–4.7)	4 (2.6–4.6)	4 (2.1–4.7)	0.713
Preoperative HbA1c levels (%), median (range)	6.4 (5.0–11.5)	6.2 (5.0–11.5)	6.9 (5.6–10.0)	0.216
Operative time (min), median (range)	399 (159–668)	395 (159–668)	404 (243–620)	0.519
Portal vein resection, n (%)	14 (33)	10 (43)	4 (21)	0.125
Other organ resections, n (%)	10 (23)	7 (30)	3 (16)	0.267
Intraoperative blood loss (mL), median (range)	1629 (176–7943)	1482 (176–6802)	1672 (338–7943)	0.343
Intraoperative blood transfusion, n (%)	31 (74)	17 (74)	14 (74)	0.987
Pathological tumor size (mm), median (range)	22 (9–98)	25 (14–98)	21 (9–60)	0.311
Number of tumors, n (%)				
1	36 (86)	19 (83)	17 (89)	0.527
2	6 (14)	4 (17)	2 (11)	
Differentiation, n (%)				
Well/moderate	36 (86)	18 (79)	18 (95)	0.208
Poor/undifferentiated	5 (12)	4 (17)	1 (5)	
Missing data	1 (2)	1 (4) ^a	0	
pT3 ^b , n (%)	34 (81)	19 (83)	15 (79)	0.764
pN, positive, n (%)	20 (48)	12 (52)	8 (42)	0.516
Microscopic lymphatic invasion, positive, n (%)	21 (50)	14 (61)	7 (37)	0.121
Microscopic vascular invasion, positive, n (%)	15 (36)	12 (52)	3 (16)	0.014
Perineural invasion, positive, n (%)	31 (74)	16 (70)	15 (79)	0.491
pStage I/II–IV ^b , n (I/II/III/IV)	7/35 (7/32/0/3)	3/20 (3/19/0/1)	4/15 (4/13/0/2)	0.488
R0 resection, n (%)	34 (81)	18 (78)	16 (84)	0.625
Clavien-Dindo classification ≥ Grade IIIa, n (%)	6 (14)	2 (9)	4 (21)	0.255
Postoperative hospital stays (days), median (range)	24 (7–113)	23 (7–113)	27 (10–111)	0.260

(Continues)

TABLE 1 | (Continued)

Factors	Total (n = 42)	Planned TP group (n = 23)	Unplanned TP group (n = 19)	p
Initiation of postoperative adjuvant chemotherapy, n (%)	19 (45)	10 (43)	9 (47)	0.801
Completion of postoperative adjuvant chemotherapy, n (%)	15 (36)	6 (26)	9 (47)	0.152

^aMissing data (n = 1).

^bBased on the American Joint Committee on Cancer/Union for International Cancer Control TNM classification, 7th edition [21].

pathological findings of the first cancer-positive pancreatic resection margin during pancreatectomy, the 13 patients were classified into three groups (high-grade PanIN type [n = 4], stromal invasion type [n = 4], and mixed type [n = 5]; Figure 3). Kaplan–Meier survival analysis showed no significant differences in OS ($p = 0.538$ and 0.778) and RFS ($p = 0.657$) among the three groups (Figure 4).

4 | Discussion

We investigated the prognostic factors for TP in patients with PDAC and the differences in prognosis with related factors between planned and unplanned TP. Our findings showed that an unplanned TP had a significantly better prognosis than a planned one. Additionally, a planned TP and not receiving or completing postoperative AC were poor prognostic factors for OS. To the best of our knowledge, this is the first study to investigate the prognosis and related factors for PDAC for planned and unplanned TP.

The gold standard for the surgical treatment of PDAC is complete surgical resection, which is an important prognostic factor for recurrence and survival. In large-scale studies, positive surgical margins have been shown to predict poor survival after resection for PDAC [11, 15]. There are various margin-positive statuses, including the retroperitoneal, bile duct, pancreatic neck, duodenal, and major visceral vessels. Among them, additional pancreatic resection up to TP in cases of a cancer-positive pancreatic resection stump, when technically feasible, may obtain an R0 resection. There has been much discussion regarding the validity of additional pancreatic resection due to a cancer-positive pancreatic resection stump for PDAC. One retrospective study showed that a positive IFS analysis is a poor prognostic factor after PD for PDAC [18]. Another retrospective study revealed that survival after PD is not improved by extending the pancreatic resection to achieve a negative margin after IFS analysis [13, 18, 19]. By contrast, additional pancreatic resection after R0 resection reportedly contributes to a prolonged prognosis [14, 16]. However, the problem seems to lie in the fact that these conflicting studies have included only a small number of cases wherein pancreatectomy was extended to TP. Only for converting TP cases, Schmidt et al. claimed that conversion of PD to TP to achieve an R0 resection in patients with PDAC improved prognosis compared with R1 resection PD [17]. At our institution, TP is routinely performed when the remnant pancreas cannot be preserved because of a cancer-positive pancreatic resection stump in IFS and permanent section analysis based on the belief that R0 resection prolongs the prognosis. Hence, there were no cases of PD or DP for R1 resection owing to a cancer-positive pancreatic resection

stump, and only TP cases were included and analyzed in this study. In the present study, an unplanned TP had an extremely favorable OS and RFS compared with a planned TP, and approximately 90% of patients in the unplanned TP group had a cancer-positive pancreatic resection stump. The pathological findings of a cancer-positive pancreatic resection stump were investigated and categorized into three types. Although there were no significant prognostic differences for each pathological type with cancer-positive pancreatic resection stumps, further large-scale analyses are needed to validate these findings. Therefore, this study supports a rigorous approach to margin clearance in TP to achieve an R0 resection for any cancer-positive pancreatic resection stump.

In recent years, owing to remarkable advances in surgical techniques and perioperative management, including insulin therapy and pancreatic enzyme supplementation, many studies have shown a prolonged prognosis of TP for PDAC, which is comparable to that of PD [2, 6–9]. A large retrospective study using data from the National Cancer Database in the United States reported that the MST of 2852 patients undergoing TP for PDAC was 15 months [6]. Another retrospective multicenter study reported an MST of 17 months for 45 patients undergoing TP for PDAC [9]. In the present study, the MST for all patients who underwent TP for PDAC was 20 months. Although patient background, including resectability status, differed between the studies, the prognosis of TP for PDAC at the institution was acceptable and comparable to those reported in these studies. We found that there was a significant difference in the prognosis between the unplanned and planned TP groups. Specifically, there were no significant differences in baseline characteristics, that is, tumor size, nodal involvement, tumor stage, or operative details between the groups. In addition, a clear difference in microscopic vascular invasion was identified, suggesting a potential difference in tumor biology. Previous studies have also demonstrated that microscopic lymphovascular invasion is associated with poor prognosis in PDAC [26–28]. Interestingly, this was the only biological parameter showing a difference between the groups. This may reflect the influence of tumor location or other unmeasured biological factors. Further prospective studies with larger cohorts are warranted to validate this hypothesis. Apart from a higher incidence of microscopic vascular invasion in the planned TP group, other clinicopathological features did not differ significantly between the two groups. We initially hypothesized that tumors in the planned TP group would be larger and more advanced than those in the unplanned TP group, as planned TP is typically indicated for extensive disease based on preoperative imaging. However, no other

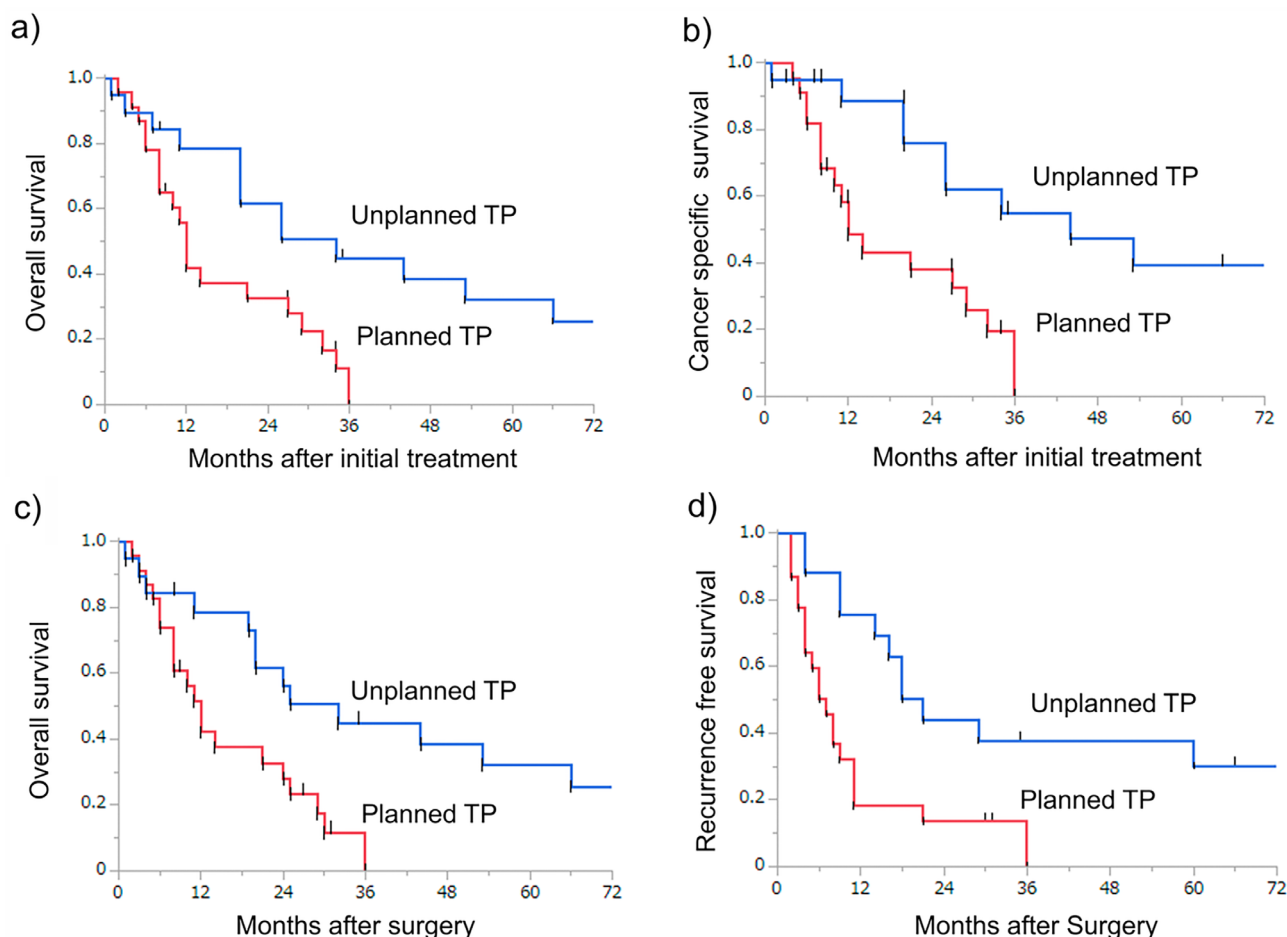


FIGURE 2 | Overall survival (OS) after initial treatment (a), cancer specific survival (b) after initial treatment, OS after surgery (c), and recurrence-free survival (RFS) (d) between the planned and unplanned total pancreatectomy (TP) groups. The unplanned TP group had significantly better OS, cancer specific survival, and RFS than those of the planned TP group, respectively. (a, b, c, and d; planned TP group; $n = 23$, unplanned TP group; $n = 19$; $p = 0.009$, $p = 0.005$, $p = 0.007$, and $p = 0.003$, respectively).

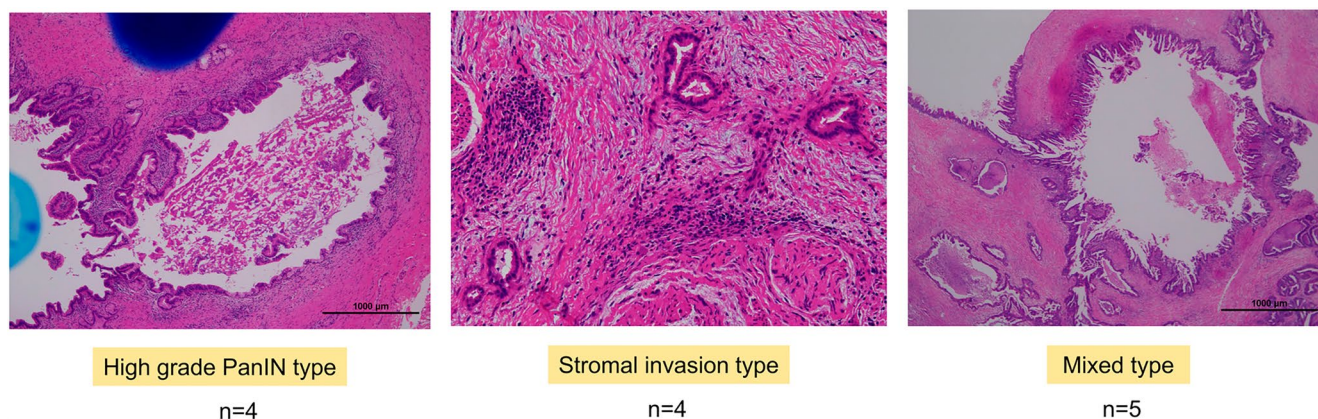
clinicopathological parameters—such as tumor size, lymph node involvement, or R0 resection rate—differed significantly between the two groups. One possible explanation for this finding is the inclusion of residual cancer cases in the planned TP group. Therefore, we further stratified the planned TP group into two subgroups: those who underwent TP for residual cancer (planned TP for remnant PDAC) and those who underwent TP for other indications (planned TP for primary PDAC), as shown in Table S2 and Figure S2. Although no statistically significant difference was observed in pathological tumor size between the two subgroups, likely due to the small sample size, the tumor size of preoperative image tended to be larger in the planned TP for primary PDAC group. Moreover, operative time, intraoperative blood loss, and the frequency of portal vein resection were all significantly greater in the planned TP for primary PDAC group, which may suggest a trend toward more locally advanced disease in these patients. However, no notable differences were observed in other clinicopathological variables or survival outcomes. These interpretations should be further examined in studies with larger patient populations. In the present study, the MST for a planned TP was only 12 months. The prognosis of a planned TP is extremely poor; further treatment strategies, including

adequate preoperative and multidisciplinary treatments, should be developed.

This study revealed that, besides a planned TP, not receiving or completing postoperative AC were independent prognostic factors for poor OS. Age, NCCN resectability status, margin status, lymph node metastasis, and postoperative AC may reportedly be independent prognostic factors of TP for PDAC [6, 8, 9]. In our cohort, factors such as age and tumor burden (including NCCN resectability status and lymph node status) were not independently associated with OS. One possible explanation is that the median age of our cohort was relatively high (approximately 70 years), which may have diminished the discriminatory power of age as a prognostic indicator. Furthermore, the overall sample size was limited, and a substantial proportion of patients presented with locally advanced disease (i.e., classified as borderline resectable or unresectable based on NCCN criteria). These characteristics may have contributed to the lack of prognostic impact observed for tumor burden. Conversely, the results are consistent with the findings of these studies that not receiving and completing postoperative AC were independent poor prognostic factors of TP for PDAC. It is well known that the completion of postoperative AC is essential for a prolonged prognosis

TABLE 2 | Univariate and multivariate analyses of poor prognostic factors.

Factors	n (%)	Univariate <i>p</i>	Hazard ratio (95% CI)	Multivariate <i>p</i>
Age (year) ≥ 75 , n (%)	14 (33)	0.955	1.45 (0.65–3.25)	0.359
Sex (male), n (%)	28 (67)	0.577		
Serum CA19-9 level at diagnosis > 37 IU/mL, n (%)	28 (67)	0.035	2.40 (0.95–6.05)	0.064
Resectability status, BR or UR, n (%)	18 (43)	0.421	1.34 (0.58–3.12)	0.488
Preoperative chemotherapy, n (%)	13 (31)	0.288		
Intraoperative blood transfusion, n (%)	31 (74)	0.778		
Planned TP, n (%)	23 (55)	0.013	2.52 (1.07–5.94)	0.035
Total remnant pancreatectomy, n (%)	9 (21)	0.144		
Pathological tumor size ≥ 20 mm, n (%)	27 (66)	0.199		
pT3, n (%)	34 (81)	0.083		
pN, positive, n (%)	20 (48)	0.038	1.26 (0.60–2.64)	0.546
pStage $\geq$ II, n (%)	35 (83)	0.096		
Portal vein resection, n (%)	14 (33)	0.914		
Clavien-Dindo $\geq$ Grade IIIa, n (%)	6 (14)	0.135		
Resection margin, R1, n (%)	8 (19)	0.309		
Postoperative adjuvant chemotherapy, none or incompleteness, n (%)	27 (64)	<0.001	3.74 (1.58–8.82)	0.003

**FIGURE 3** | Pathological findings of first cancer positive pancreatic resection margin during pancreatectomy. Thirteen patients, for whom microscopic evaluations were available, were classified into three groups (high-grade PanIN type [$n=4$], stromal invasion type [$n=4$] and mixed type [$n=5$]).

in patients with PDAC [25, 29]. Based on previous reports, the initiation rate of postoperative AC was estimated to be 60%–80% [30], the completion rate to be 70% [25], and the percentage of patients who were able to initiate and complete postoperative AC was approximately 50%. However, in this study, the initiation and completion rates of postoperative AC were 45% and 36%, respectively. Unlike PD or DP, as in previous reports [9], this study also showed a relatively lower AC completion rate in patients who underwent TP. TP causes a complete loss of pancreatic exocrine and endocrine functions compared with organ-preserving pancreatectomies such as PD or DP. Pancreatic exocrine deficiency with maldigestion and malabsorption can contribute to

a cachexia-like syndrome, which significantly decreases the QOL and physical activity [4]. Pancreatic endocrine deficiency can impair glucose tolerance and interfere with food consumption. In this study, the most common reason for not receiving or completing postoperative AC was poor physical condition, including a decreased QOL and anorexia. Patients who completed postoperative AC were compared with those who did not receive or complete postoperative AC. Although the importance of perioperative nutritional intervention has been advocated worldwide, no significant differences were found in preoperative and postoperative serum albumin levels. By contrast, none of the patients who underwent TP with a complicated resection

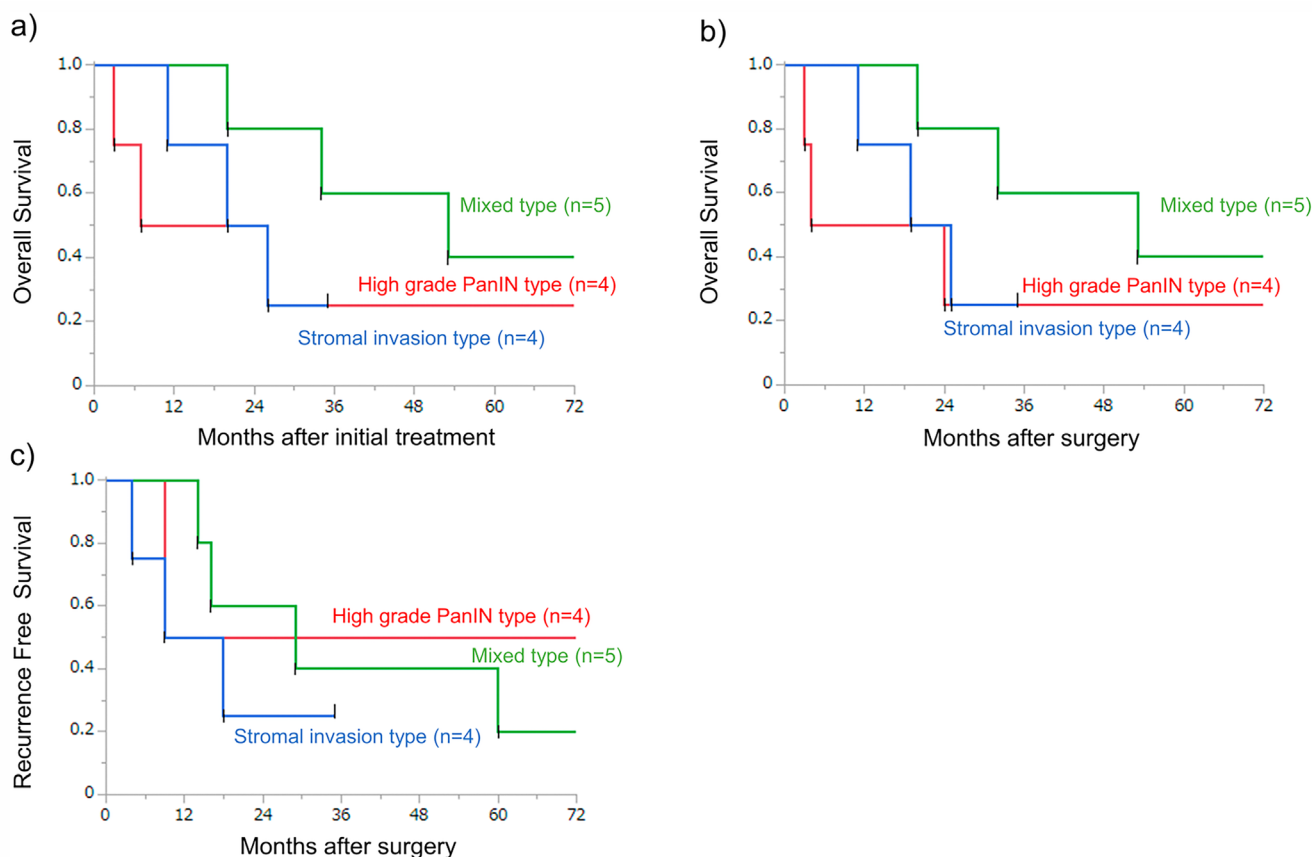


FIGURE 4 | Overall survival (OS) after initial treatment (a), OS after surgery (b), and recurrence-free survival (RFS) (c) according to the pathological type of the first cancer positive pancreatic resection margin during pancreatectomy. There was no significant difference in OS ($p=0.538$ and $p=0.778$) and RFS ($p=0.657$) among the pathological types.

of other organs suspected of invasion completed postoperative AC, and even patients with pT3 status tended not to complete AC. In these cases, postoperative AC is less likely to be initiated and completed, suggesting a focus on adequate preoperative treatment for a prolonged prognosis.

This study has some limitations. First, the primary clinical question of this study was whether conversion to TP is beneficial when a positive pancreatic margin is identified on IFS analysis. However, the design of this study did not directly compare patients who underwent conversion to TP following IFS positivity with those who did not. This is because TP is routinely performed at our institution whenever a positive pancreatic margin is confirmed on IFS or final pathology. Consequently, there were no patients with a positive margin who did not undergo TP, making such a comparison impossible in the context of our cohort. In light of the structure of our cohort, we simply compared the outcomes of patients who underwent planned TP based on preoperative assessment with those who underwent unplanned TP, prompted by intraoperative or postoperative margin positivity. Although this comparison did not fully replicate the ideal design described in previous studies such as that of Schmidt et al., we believe it nonetheless provides valuable insights into the clinical implications of unplanned TP. We acknowledge this as a limitation of our study and suggest future multicenter studies to enable a more direct and comprehensive evaluation of this important clinical question. Second, this was a single-center retrospective study with a relatively small number of patients. Third, converting PD/DP to TP depends on the discretion

of the physician when the remnant pancreas is too small to reconstruct in PD cases or when the preservation of the remnant pancreas is impossible due to invasion of the gastroduodenal artery in DP cases. Hence, the findings of this study need to be confirmed in a large prospective study.

In conclusion, an unplanned TP has a significantly better prognosis than a planned TP. This study supports a rigorous approach to margin clearance for TP in PDAC to achieve an R0 resection in a cancer-positive pancreatic resection stump. However, the prognosis of patients undergoing a planned TP for PDAC is extremely poor, and adequate preoperative and multidisciplinary treatment may be necessary to prolong the prognosis.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.