Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2022, Volume 2, Issue 2, Page No: 56-67

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Conversion Surgery Following Multidisciplinary Therapy in Unresectable Pancreatic Ductal Adenocarcinoma: Impact on Survival

Hiroto Sakurai[1*], Naoki Tamura[1], Yuna Morimoto[1], Airi Kinoshita[1]

[1]Department of Surgery, Kansai Medical University, Hirakata 573-1010, Japan.

***E-mail** ✉ Kinoshitaairi.jp@yahoo.com

Received: 07 May 2022; **Revised:** 12 September 2022; **Accepted:** 14 September 2022

ABSTRACT

Patients diagnosed with pancreatic ductal adenocarcinoma that is initially deemed unresectable face a very poor prognosis. Conversion surgery, performed after tumor shrinkage or favorable response to therapy, has emerged as a potential intervention to improve survival. This study examines the outcomes and prognostic factors associated with this approach. We retrospectively analyzed cases of pancreatic ductal adenocarcinoma referred for possible surgery at our institution between January 2006 and December 2019. Conversion surgery was reserved for patients with unresectable tumors who were considered capable of achieving complete (R0) resection. Survival outcomes and factors affecting overall survival were evaluated in patients undergoing surgery after initial systemic therapy.

The study included 638 patients with advanced disease. Among them, 180 were initially resectable, 60 were borderline resectable, 252 were locally advanced and unresectable, and 146 had distant metastases. Conversion surgery was ultimately performed in 20 of the 398 patients with unresectable disease (5.1%). The median interval from the start of therapy to surgery was 15.5 months. Treatment responses assessed by RECIST showed one complete response, 13 partial responses, five stable disease cases, and one progression. Pathological evaluation confirmed tumor downstaging in all operated patients. Tumor regression assessed by the Evans system revealed grade I in four patients, grade IIb in seven, grade III in seven, and grade IV in two. Median overall survival calculated from initial treatment was 73.7 months for patients who underwent conversion surgery, compared with 32.7 months for initially resectable, 22.7 months for borderline resectable, 15.7 months for locally advanced unresectable, and 8.8 months for metastatic patients. Multivariate analysis identified receipt of chemoradiotherapy and achieving a partial or complete response by RECIST as significant predictors of improved survival ($p = 0.004$ and 0.03, respectively). In patients with initially unresectable pancreatic ductal adenocarcinoma, conversion surgery following multimodal therapy, including chemoradiotherapy, can offer substantial survival benefits. Early identification of candidates and coordinated multidisciplinary care are critical to maximize the clinical impact of this approach.

Keywords: Pancreatic ductal adenocarcinoma, Conversion surgery, Chemoradiotherapy, Multidisciplinary therapy

How to Cite This Article: Sakurai H, Tamura N, Morimoto Y, Kinoshita A. Conversion Surgery Following Multidisciplinary Therapy in Unresectable Pancreatic Ductal Adenocarcinoma: Impact on Survival. Asian J Curr Res Clin Cancer. 2022;2(2):56-67. https://doi.org/10.51847/qjdh5lf4TF

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is among the most lethal cancers in Japan, with very limited survival prospects [1]. In the United States, it ranks as the fourth leading cause of cancer-related death [2]. Overall, the 5-year survival rate for PDAC remains near 10%, and surgical removal of the tumor is currently the only potential curative treatment. Unfortunately, only a small fraction of patients—roughly 10–20%—are candidates for resection at initial diagnosis [3].

Treatment strategies for PDAC are increasingly guided by tumor resectability rather than traditional staging systems. The NCCN has established recommendations based on resectability, guiding therapy for each category

[4]. For patients with unresectable locally advanced (UR-LA) or metastatic (UR-M) disease who maintain adequate performance status, systemic chemotherapy is the standard approach. Common regimens include FOLFIRINOX (or modified FOLFIRINOX), gemcitabine with nab-paclitaxel, and chemoradiotherapy.

In 2019, the Japanese Pancreas Society updated its resectability criteria for PDAC, aligning closely with NCCN guidance [5]. Evidence from a Japanese prospective trial suggests that, in locally advanced PDAC invading surrounding vessels, surgical resection can confer a survival advantage over chemoradiotherapy alone [6].

Recent advances in multimodal treatment—combining surgery, chemotherapy, and chemoradiation—have improved outcomes for PDAC patients [7–9]. Adjuvant chemotherapy is now standard after curative surgery in resectable cases [10, 11], and neoadjuvant therapy is increasingly employed. Notably, some patients with initially unresectable disease respond sufficiently to therapy to allow surgical resection, a procedure referred to as "conversion surgery." Multiple studies have explored the outcomes and survival benefits of this strategy in carefully selected UR-PDAC patients [12–22]. Despite these findings, the extent to which conversion surgery improves long-term outcomes remains uncertain.

The present study investigates the survival benefits of conversion surgery and identifies prognostic factors in UR-PDAC patients treated with chemoradiotherapy.

Materials and Methods

Ethical considerations

This study adhered to institutional guidelines and the Declaration of Helsinki. All participants provided written informed consent for the use of their medical data.

Study design and patient selection

We conducted a retrospective analysis using a prospectively maintained database of patients with PDAC treated at Kagoshima University's Department of Digestive Surgery, Breast and Thyroid Surgery, between January 2006 and December 2019. PDAC was confirmed via cytology or histopathology obtained through endoscopic retrograde cholangiopancreatography or endoscopic ultrasound-guided fine-needle aspiration. Disease staging and progression were assessed using multidetector-row CT, ethoxybenzyl-enhanced MRI, and FDG-PET imaging.

Patients were classified as resectable (R), borderline resectable (BR), unresectable locally advanced (UR-LA), or unresectable metastatic (UR-M) according to the 2020 NCCN Clinical Practice Guidelines version 2 [4]. Conversion surgery was considered only for patients with initially unresectable tumors who responded sufficiently to therapy to allow complete resection (R0).

Treatment regimens

Patients received one of several chemotherapy protocols depending on clinical indications. The gemcitabine and S-1 (GS) regimen involved oral administration of S-1 at 60 mg/m² twice daily on days 1–14, combined with intravenous gemcitabine 1000 mg/m² on days 8 and 15 of a 21-day cycle. The gemcitabine plus nab-paclitaxel (GEM + nab-PTX) regimen consisted of gemcitabine 1000 mg/m² and nab-paclitaxel 125 mg/m² administered intravenously on days 1, 8, and 15 of a 28-day cycle.

Modified FOLFIRINOX (m-FOLFIRINOX) was administered according to a Japanese phase II protocol. Oxaliplatin (85 mg/m²) and leucovorin (200 mg/m²) were given sequentially as 2-hour infusions, followed by irinotecan (180 mg/m²) over 90 minutes through a bypass line. Finally, 5-fluorouracil was given as a 400 mg/m² bolus, followed by continuous infusion of 2400 mg/m² over 46 hours, repeated every 2 weeks.

For chemoradiotherapy (CRT), patients received hyperfractionated accelerated radiotherapy concurrently with S-1 at 80 mg/m² for 21 days, delivering a total of 50–58 Gy over 40 fractions across 4 weeks. Following CRT, S-1 was administered in cycles of 2 weeks on, 2 weeks off. The GEM + nab-PTX and m-FOLFIRINOX regimens have been approved in Japan for unresectable pancreatic cancer since December 2014 and have been used in practice since then.

Conversion surgery

Indications for conversion surgery were determined at a multidisciplinary tumor board, including pancreatic surgeons, medical oncologists, radiologists, and pathologists. Only patients demonstrating sufficient tumor

shrinkage to allow complete resection, including major vessels and any controllable metastatic sites, were considered. Candidates also required a period of disease control and either absence of metastasis or metastasis manageable through surgery.

Adjuvant therapy

Postoperative adjuvant therapy was generally offered to patients in good physical condition. When new lesions appeared after conversion surgery, re-resection was considered if feasible.

Evaluation of treatment response

Radiologic responses were assessed using RECIST version 1.1, and the pathological response was graded according to the Evans system. R0 resection was defined as complete removal of the tumor with negative margins. Postoperative complications were classified using the Clavien–Dindo system, and mortality was defined as death within 90 days of surgery.

Statistical analysis

Categorical data were analyzed using chi-square or Fisher's exact tests, as appropriate. Kaplan–Meier analysis was used to estimate survival curves, with differences evaluated by the log-rank test. Overall survival (OS) was defined as the interval from initial therapy to death from any cause, and progression-free survival (PFS) as the time from initial therapy to documented disease progression. Univariate Cox proportional hazards models were used to identify potential prognostic factors for OS, and variables with $p < 0.05$ were included in multivariate models. Hazard ratios and 95% confidence intervals were reported. Statistical analyses were conducted using SigmaPlot version 12.5 (HULINKS, Tokyo, Japan).

Results and Discussion

Patient characteristics

A total of 638 patients were included during the study period. Among these, 180 were classified as resectable (R), 60 as borderline resectable (BR), 252 as unresectable locally advanced (UR-LA), and 146 as unresectable metastatic (UR-M). The subset of 398 patients with initially unresectable disease was analyzed for conversion surgery outcomes. Twenty patients (5.0%) underwent conversion surgery, including 9 with UR-LA and 11 with UR-M disease. Clinical characteristics of patients who did and did not undergo conversion surgery are summarized in **Table 1**.

Table 1. A comparison of the clinical characteristics between CS and non-CS patients.

Variables	Conversion Surgery		p-Value
	(+) (n = 20)	(−) (n = 378)	
age (years), median (range)	65 (44–83)	69 (33–87)	0.25
gender (M/F), n	(10/10)	(207/171)	0.656
tumor location (Ph/Pb,Pt), n	(14/6)	(218/160)	0.282
unresectability status (UR-LA vs UR-M), n	(9/11)	(243/135)	0.622
CEA, median (range) (U/mL)	3.4 (1.1–9.4)	4.0(0.3–845)	0.51
CA19-9, median (range) (U/mL)	2577 (0.6–1985)	211(0.6–50,000)	0.17
tumor size, median (range) (mm)	30 (18–50)	35(8–116)	0.323
T(4/3), n	(16/4)	(332/46)	0.385
N(1/0), n	(7/13)	(136/252)	0.917
M(1/0), n	(11/9)	(197/181)	0.829

M, male; F, female; CS, conversion surgery; Ph, pancreatic head; Pb, pancreatic body; Pt, pancreatic tail; UR-LA, unresectable locally advanced cancer; UR-M, unresectable cancer with metastasis. T, N, and M were classified according to the Tumor-Node-Metastasis (TNM) classification.

No significant differences were observed between patients who underwent conversion surgery and those who did not in terms of age, sex, tumor location (pancreatic head versus body/tail), initial unresectability classification (UR-LA versus UR-M), pre-treatment serum levels of carcinoembryonic antigen (CEA) or cancer antigen 19-9

(CA19-9), tumor size, or TNM staging (T-, N-, and M-categories). The detailed clinical profiles of the 20 patients who received conversion surgery are summarized in **Figures 1 and 2**, as well as in **Tables 2 and 3**.

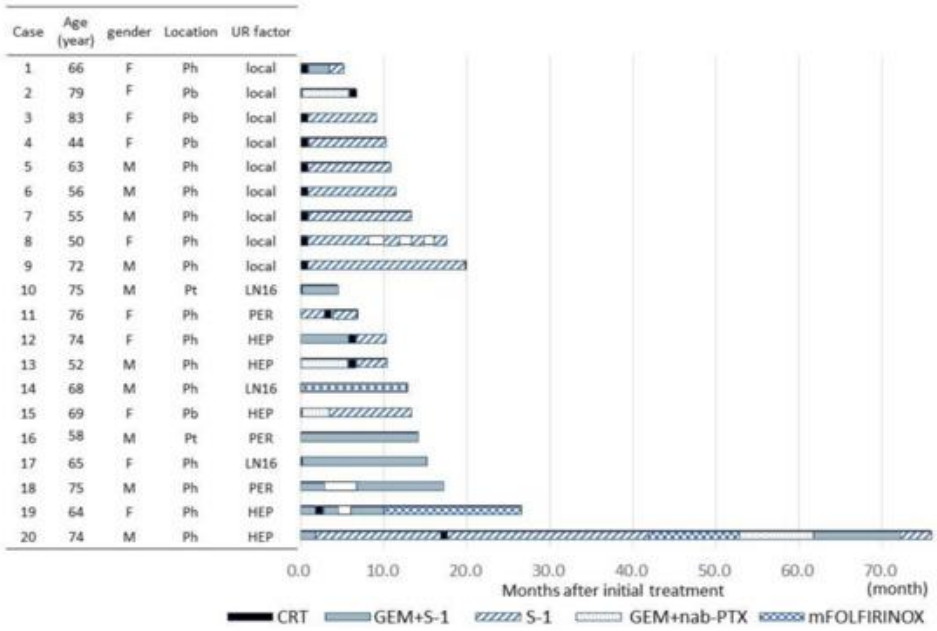

Figure 1. Overview of clinical characteristics and preoperative treatments for the 20 patients who underwent conversion surgery. Abbreviations: UR-LA, unresectable locally advanced pancreatic cancer; UR-M, unresectable metastatic pancreatic cancer; M, male; F, female; Ph, pancreatic head; Pb, pancreatic body; Pt, pancreatic tail; LN16, para-aortic lymph node metastasis; PER, peritoneal dissemination; HEP, liver metastases; CRT, chemoradiotherapy; GEM, gemcitabine; S-1, oral S-1; nabPXL, nab-paclitaxel; mFOLFIRINOX, modified FOLFIRINOX (combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin).

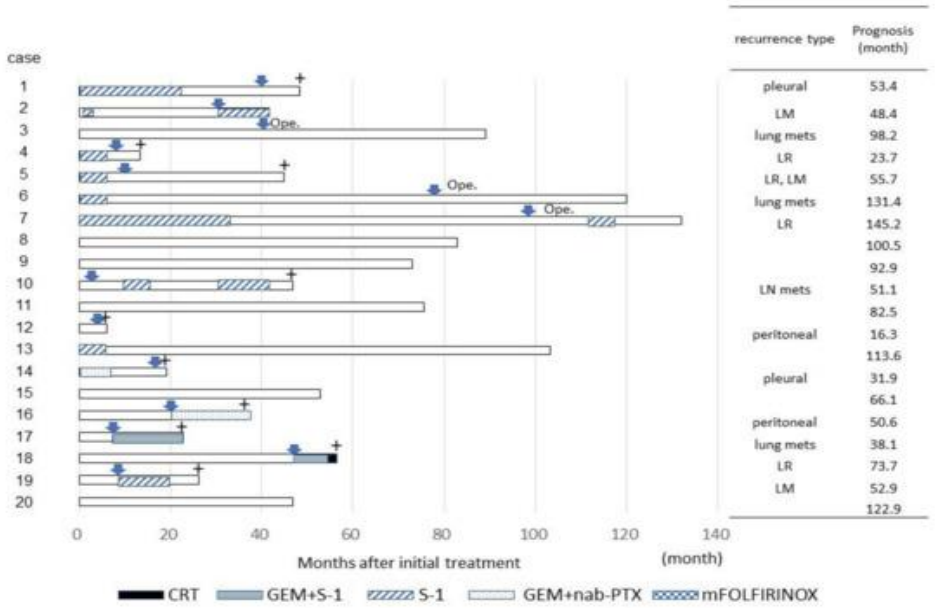

Figure 2. Clinical profiles of the 20 patients following conversion surgery, including post-operative treatments and outcomes. Abbreviations: pleural, pleural dissemination; LM, liver metastasis; lung mets, lung metastasis; LR, local recurrence; peritoneal, peritoneal dissemination; directing arrow, time period of recurrence or metastasis; Ope, additional surgery; +, time of death.

Table 2. Clinical characteristics of 20 patients who underwent conversion surgery.

Case	CEA (U/mL, Before)	CEA (U/mL, After)	CA19-9 (U/mL, Before)	CA19-9 (U/mL, After)	Tumor Size (mm, Before)	Tumor Size (mm, After)	Treatment Effect (RECIST)	Operative Method	Operative Time (min)	Bleeding Volume (mL)	Hospital Stay (Day)
1	2.4	2	25.9	9.9	27	13	PR	SSPPD	678	295	32
2	2.6	3.3	55.9	39	33	13	PR	DP	403	160	22
3	8	10.3	2789	24.9	32	23	PR	DP	373	260	50
4	1.1	5.1	81.4	34	50	50	SD	DP	438	1150	9
5	2.9	3.1	5103	19.9	23	12	PR	SSPPD + PVR	509	1250	11
6	9.4	4.4	92	10.9	29	13	PR	SSPPD	575	1220	23
7	6.4	2.4	253.5	49.6	24	9	PR	SSPPD + PVR	738	3010	16
8	2	2.7	9.2	11.4	42	10	PR	SSPPD	464	1030	10
9	1.5	1.6	1559	11.2	41	9	PR	SSPPD + PVR	574	1665	13
10	2.3	2.2	67.4	9	21	10	PR	DP	408	1075	11
11	3.4	3	20.6	7.4	30	16	PR	SSPPD + PVR	643	1390	9
12	2.5	3.2	1985	48.2	24	12	SD	SSPPD + HPR	841	2340	11
13	3.8	4.2	270	38.1	29	8	PR	SSPPD	729	2470	16
14	4.6	8	1515	16.4	41	34	PR	SSPPD + PVR	919	3600	47
15	5.1	3	1846	13.3	35	0	CR	DP	391	240	23
16	3.4	3.4	5.2	10.4	21	19	SD	DP	352	90	8
17	8	8.4	0.6	0.6	18	13	SD	SSPPD	623	1040	13
18	3	4.6	1047	10.7	32	11	PR	SSPPD	550	1020	8
19	1.8	2.1	516	17.8	30	9	PD	TP + PVR + HPR	613	460	14
20	2.9	9.5	330	99	24	25	SD	SSPPD + PVR	641	1695	13

UR-LA, unresectable locally advanced cancer; UR-M, unresectable cancer with metastasis; before, before initial therapy; after, after various therapy; PR, partial response; SD, stable disease; PR, partial response; SSPPD, substomach preserving pancretoduodenectomy; DP, distal pancreatectomy; PVR, portal vein resection; HPR, hepatic partial resection; TP, total pancreatectomy.

Table 3. Clinical characteristics of 20 patients who underwent conversion surgery. Each stage was classified according to the TNM classification.

Case	Stage (Before)	Stage (After)	p-Stage	Pathological	Evans
1	3	3	2a	tub2	IIb
2	3	2a	2a	tub1	I
3	3	3	2b	tub2	III
4	3	2b	2a	muc	IIb
5	3	2a	2a	tub1	IIb
6	3	1a	1	por	III
7	3	3	2b	tub1	III
8	3	3	2a	similar to NEN	IIb
9	3	3	1	tub2	IIb
10	4	3	0	no neoplasm	IV
11	4	2a	2a	tub1	III
12	4	2a	2a	tub2	I
13	4	2b	1	a few	III
14	4	4	2a	tub2	IIb
15	4	0	0	no neoplasm	IV

16	4	2a	2b	tub1	I
17	4	2a	1	tub1	III
18	4	3	2b	tub2	III
19	4	4	4	tub2	IIb
20	4	3	2a	tub2	I

UR-LA, unresectable locally advanced cancer; UR-M, unresectable cancer with metastasis; before, before initial therapy; after, after various therapy; p-stage, pathological stage; tub1, tubular adenocarcinoma with high differentiation; tub2, tubular adenocarcinoma with moderate differentiation; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma; NEN, neuroendocrine neoplasm; a few, a few neoplasms; Evans, Evans classification.

Among the 11 patients initially classified as UR-M, five had liver metastases, three had peritoneal dissemination, and three had para-aortic lymph node metastases at diagnosis. Histological confirmation was obtained for all peritoneal and para-aortic metastases, while only two of the five patients with liver metastases underwent histological verification.

The median interval from initial treatment to conversion surgery was 10.8 months (range 5.1–19.9) for patients with UR-LA and 13.3 months (range 4.4–75.9) for those with UR-M, with no significant difference between the groups. The preoperative treatment strategies differed across patients. All UR-LA patients received CRT, which served as the initial therapy in all but one patient (case 2), who received CRT following induction chemotherapy with gemcitabine plus nab-paclitaxel. Patients with UR-M underwent various chemotherapy regimens, and five also received CRT for local disease control. Post-treatment evaluation by RECIST indicated one complete response (CR), 13 partial responses (PR), five stable disease (SD), and one progressive disease (PD).

Serum CA19-9 levels were significantly lower at the time of conversion surgery compared with baseline values (median 16.4 U/mL, range 0.6–99 vs. median 156 U/mL, range 0.6–1985; $p = 0.0065$), whereas CEA levels did not change significantly ($p = 0.418$). Tumor size also decreased significantly, with a median of 13 mm at surgery compared with 30 mm at diagnosis ($p < 0.001$). In cases 6, 17, and 19, reductions were observed in CEA, CA19-9, and tumor size following treatment **(Table 2)**.

Regarding surgical procedures, 13 patients underwent substomach-preserving pancreaticoduodenectomy, including six with portal vein resection (PVR) and one with hepatic resection (HPR). Distal pancreatectomy was performed in six patients, and one patient underwent total pancreatectomy with PVR and HPR. The median operative time was 575 minutes (range 352–919), median blood loss 1150 mL (range 90–3600), and median postoperative hospital stay 13 days (range 8–50). Major postoperative complications (Clavien–Dindo IIIa) occurred in three patients—chylous ascites, interstitial pneumonia, and intra-abdominal abscess (cases 1, 3, and 14)—prolonging hospital stays beyond one month. There were no perioperative deaths, and R0 resection of the primary tumor was achieved in all cases.

Comparing clinical stages before and after therapy, 13 patients were downstaged clinically and 19 pathologically. Residual tumors consisted of highly differentiated tubular adenocarcinoma in six patients and moderately differentiated tubular adenocarcinoma in eight. Evans grading showed grade I in four patients (20%), IIb in seven (35%), III in seven (35%), and IV in two (10%). Pathological complete response (pCR) was achieved in two cases (cases 10 and 16), while one case (case 20) could not be fully evaluated due to minimal residual tumor. Among the two patients who underwent combined hepatic resection and pancreatectomy, one had residual cancer in the liver specimen.

Adjuvant chemotherapy

Following conversion surgery, adjuvant chemotherapy was administered to eight patients (40%), all receiving S-1. The remaining 12 patients did not receive postoperative chemotherapy due to factors such as reduced performance status, significant surgical complications, advanced age, or patient preference. Disease recurrence was observed in 14 patients (70%). Patterns of recurrence included peritoneal dissemination in four patients, local recurrence (including newly developed tumors in the remnant pancreas) in three, liver metastases in three, lung metastases in three, and lymph node involvement in one patient. Three of these patients underwent further surgical intervention to remove recurrent lesions: two for pulmonary metastases and one for a metachronous pancreatic tumor, occurring 41, 78, and 97 months after the initial conversion surgery, respectively (cases 3, 6, and 7; **(Figure 2)**).

Comparison of overall survival from the initiation of first-line therapy between patients with initially unresectable locally advanced disease and those with metastatic disease revealed no statistically significant difference (median survival not reached vs. 52 months; p = 0.20) **(Figure 3)**.

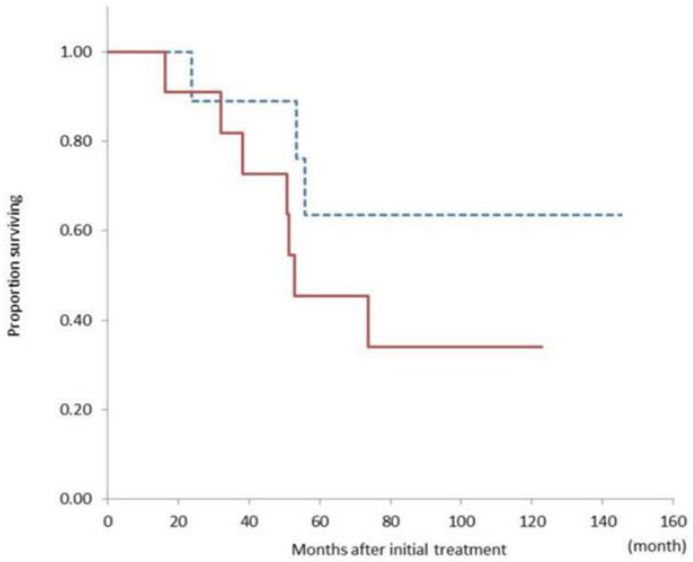

Figure 3. Comparison of the overall survival curves between patients with unresectable locally advanced cancer (dashed line, n = 9) and unresectable cancer with metastasis (solid line, n = 11) who underwent conversion surgery. There is no significant difference in overall survival between the groups (p = 0.20).

Figure 3 illustrates the overall survival of patients who underwent conversion surgery, comparing those with unresectable locally advanced disease (dashed line, n = 9) to those with metastatic disease (solid line, n = 11). No statistically significant difference in survival was observed between these two groups (p = 0.20).
Additionally, we analyzed overall survival from the start of initial treatment across all patient groups classified by NCCN guidelines: conversion surgery, resectable (R), borderline resectable (BR), unresectable locally advanced (UR-LA), and unresectable metastatic (UR-M). Median overall survival times were 73.7 months for the conversion surgery group, 32.7 months for R, 22.7 months for BR, 15.7 months for UR-LA, and 8.8 months for UR-M **(Figure 4)**. Survival differed significantly among these groups (p-values not **shown).**

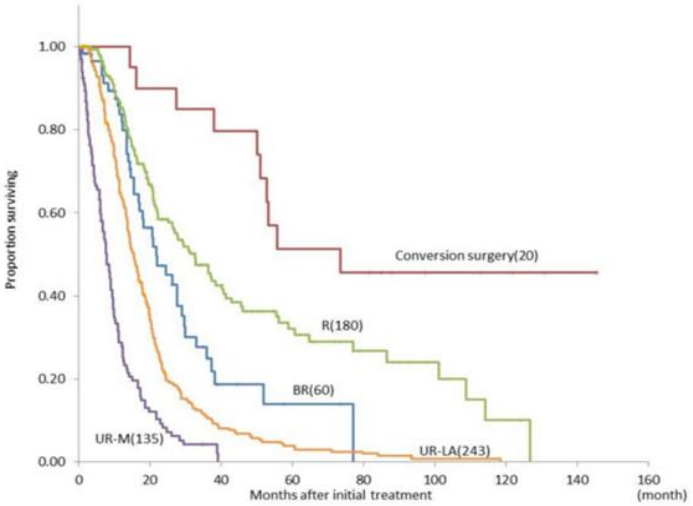

Figure 4. Comparison of the overall survival curves between patients with pancreatic ductal adenocarcinoma judged as R (n = 180), BR (n = 60), UR-LA (n = 243), or UR-M, (n = 135) according to the NCCN guideline, who underwent conversion surgery (n = 20). Abbreviations: R, resectable cancer; BR, borderline resectable cancer; UR-LA, unresectable locally advanced cancer; UR-M, unresectable cancer with metastasis; NCCN, National Comprehensive Cancer Network.

Figure 4 illustrates survival outcomes of pancreatic ductal adenocarcinoma patients categorized by NCCN resectability: 180 resectable (R), 60 borderline resectable (BR), 243 unresectable locally advanced (UR-LA), 135 unresectable with metastasis (UR-M), and 20 patients who underwent conversion surgery.

We explored factors affecting overall survival in the conversion surgery group using logistic regression. In univariate analysis, patients who received chemoradiotherapy (CRT) or exhibited tumor shrinkage classified as partial or complete response (PR/CR) per RECIST criteria had a lower risk of death compared to those who did not receive CRT or had stable/progressive disease (p = 0.002 and 0.015, respectively). Multivariate analysis confirmed that CRT and RECIST PR/CR remained significant independent predictors of better survival (p = 0.004 and 0.03).

Table 4. Predictive factors for the overall survival of patients with unresectable pancreatic cancer (univariate and multivariate logistic regression analyses).

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95%CI	p-Value	HR	95%CI	p-Value
Age (per year)	0.67	-	0.54	-	-	-
Sex (male vs. female)	0.75	0.19–2.39	0.65	-	-	-
Location (Ph vs. Pb,Pt)	1.47	0.22–2.61	0.59	-	-	-
Tumor size (> 30 mm vs. <30 mm)	0.64	0.37–5.80	0.49	-	-	-
CEA (> 3 U/mL vs. <3 U/mL)	0.32	0.18–2.27	0.32	-	-	-
CA19-9 (> 100 U/mL vs. <100 U/mL)	0.62	0.15–1.88	0.45	-	-	-
UR-M vs. UR-LA	2.38	0.18–2.16	0.21	-	-	-
CRT ((+) vs.(−))	8.06	0.61–9.24	0.002	8.54	2.03–35.97	0.004
Tumor size (> 30 mm vs. <30 mm)	0.77	2.15–30.18	0.68	-	-	-
CEA > 3 U/mL vs. <3 U/mL)	1.23	0.22–2.69	0.76	-	-	-
CA19-9 (> 100 U/mL vs. <100 U/mL)	0.35	0.32–4.80	0.32	-	-	-
Change of tumor size (> 0.5 v.s. <0.5)	0.72	0.04–2.74	0.61	-	-	-
Change of CEA	1.5	0.20–2.55	0.56	-	-	--
Change of CA19-9	1	0.39–5.83	1	-	-	-
RECIST (PD,SD vs. PR,CR)	4.93	0.12–7.91	0.015	5.05	1.20-21.25	0.03
Period until operation (> 12 m vs. <12 m)	0.89	1.37–17.72	0.86	-	-	
Operation time (> 600 min vs. <600 min)	1.36	0.26–3.09 0.39–4.70	0.63	-	-	-
Bleeding volume (> 1000 mL vs. <1000 mL)	0.89	0.23–3.52	0.87	-	-	-
Evans (I-IIa vs. IIb-V)	0.57	0.12–2.76	0.49	-	-	-
pT (1,2 vs.3,4)	2.14	0.55–8.31	0.27	-	-	-
LN mets ((+) vs.(−))	0.77	0.16–3.67	0.75	-	-	-
Adjuvant chemo. ((−) vs(+))	2.07	0.53–8.10	0.29	-	-	-

HR, hazard ratio; CI, confidential interval; Ph, pancreatic head; Pb, pancreatic body; Pt, pancreatic tail; UR-LA, unresectable locally advanced cancer; UR-M, unresectable cancer with metastasis; CRT, chemoradiotherapy; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; LN mets, lymph node metastasis.

Interest in conversion surgery for locally advanced pancreatic cancer has grown steadily since the 2010s [12–22]. Current NCCN guidelines (v1.2021) suggest that surgical resection can be considered in patients with good performance status and no disease progression following first-line therapy [4]. Our retrospective analysis indicates that conversion surgery for patients with UR-PDAC is both feasible and relatively safe, with no perioperative deaths and a low rate of severe complications (Clavien–Dindo class ≥ IIIa, 15%). These findings suggest potential for improved long-term survival in selected patients.

In this study, only 5% of patients with unresectable disease underwent conversion surgery (UR-LA, 3.6%; UR-M, 7.5%), which is lower than reported in many previous studies. This may reflect our institution's conservative approach to selecting patients for surgery following multidisciplinary therapy [16]. Earlier studies often focused on patients who exhibited exceptional responses to palliative therapy, resulting in higher resection rates. For

example, Hackert *et al*. reported that 292 of 575 patients (50.8%) with locally advanced PDAC who received neoadjuvant therapy underwent surgery [7]; however, the median survival after resection was only 15.3 months. In contrast, our study demonstrated a median overall survival of 73.7 months following conversion surgery, suggesting that careful patient selection can yield substantial survival benefits. For patients with UR-LA and UR-M who did not undergo resection, median survival durations were similar to previously reported values (15–17 months and 8.8 months, respectively). Other studies, such as that by Lee *et al*., have shown excellent survival outcomes for a subset of UR-LA patients undergoing conversion surgery, highlighting the potential impact of selection criteria on both resectability rates and survival [23].

Conversion surgery appears to markedly improve prognosis for UR-PDAC patients, even in comparison with patients initially considered resectable. In our cohort, there was no significant survival difference between UR-LA and UR-M patients who underwent conversion surgery. Multivariate analysis identified tumor response by RECIST (CR/PR) following therapy as a key prognostic factor, underscoring the importance of achieving tumor shrinkage through multidisciplinary approaches prior to surgery. Despite these benefits, recurrence remains common, occurring in 70% of patients, with 30% experiencing relapse within the first year.

Adjuvant chemotherapy after conversion surgery was administered in only 40% of patients, primarily due to poor performance status, perioperative complications, advanced age, or patient refusal. Prior studies suggest that adjuvant therapy may not be necessary for all patients who have received neoadjuvant treatment, with benefits largely confined to those with node-positive disease [10, 24]. Minimizing surgical morbidity may therefore be crucial to increase the likelihood of postoperative therapy and reduce early recurrence rates [25]. Furthermore, our follow-up showed that additional resection of isolated metastases, including lung lesions and remnant pancreatic tumors, can offer long-term survival opportunities [26, 27].

Previous multicenter studies, such as that by Satoi *et al*., have reported improved survival in patients undergoing conversion surgery, with optimal timing around 240 days after initial therapy [13]. Favorable prognostic factors included sufficient gemcitabine dosage, reductions in tumor markers prior to surgery, and RECIST PR/CR evaluations. Similarly, Michelakos *et al*. identified preoperative CA19-9 levels >100 U/mL and time intervals >8 months between diagnosis and surgery as predictors of shorter disease-free survival in BR/locally advanced PDAC treated with FOLFIRINOX [28], highlighting the ongoing debate about the best timing for conversion surgery.

Histopathological assessment using the Evans grading system remains an important prognostic tool [19, 29–32]. In our series, grades IIb, III, and IV, indicating >50% tumor destruction, were observed in 16 of 20 patients. Residual tumors tended to display a high proportion of well-differentiated cells, suggesting that poorly differentiated cells may be particularly susceptible to chemoradiotherapy.

In summary, our findings indicate that chemoradiotherapy and tumor response (RECIST CR/PR) are critical prognostic indicators for UR-PDAC patients undergoing conversion surgery. Combination therapy with S-1 and radiation has shown promising tolerability and survival outcomes [33]. Evidence from neoadjuvant trials in BR-PDAC, including gemcitabine-based chemoradiation, further supports the value of preoperative therapy in improving surgical outcomes [34]. While the LAP-07 trial did not demonstrate a survival benefit for CRT compared to chemotherapy alone, it did reduce local progression without increasing severe toxicity, suggesting a potential role for CRT in the context of conversion surgery [35].

In our cohort, no significant difference in overall survival was observed between UR-LA and UR-M patients who underwent conversion surgery. This finding aligns with previous results reported by Yanagimoto *et al*., who also found comparable outcomes between these two patient groups [18]. Reports on pancreatic resection in patients with synchronous metastases remain limited. Wright *et al*. described 23 cases of stage IV pancreatic cancer patients who underwent surgical resection after a favorable response to systemic chemotherapy, with metastatic sites including the liver (n = 16), lung (n = 6), and peritoneum (n = 2) [36]. Among 1,147 patients with stage IV disease, the resection rate was only 2.0%, and the median survival time from diagnosis was 34.1 months. Similarly, Frigerio *et al*. reported that 24 of 535 patients (4.5%) with pancreatic cancer and liver metastases underwent combined hepatic and pancreatic resection, with a median survival of 56 months [37]. These data suggest that only a small fraction of UR-M patients—so-called “super-responders”—are candidates for conversion surgery, making the identification of reliable predictive markers for long-term survival after surgery crucial.

This study has several limitations. First, it was a single-center retrospective analysis with a limited sample size. Second, the role of conversion surgery remains controversial, even in patients achieving tumor control with CRT. While chemotherapy provides systemic disease management, surgical resection may offer local control; however, evidence to guide this approach is limited. In Japan, the PREP-04 study (UMIN000017793), a multicenter

prospective observational trial, is currently investigating the effects of conversion surgery in initially unresectable PDAC patients. Selection bias is an inherent limitation, as only patients responding favorably to initial therapy were considered for surgery. Conversion rates reported in the literature vary widely: 28.6% with FOLFIRINOX according to Nitsche *et al*. [38], and up to 50.8% in Hackert *et al*. [7]. Currently, FOLFIRINOX or gemcitabine plus nab-paclitaxel are recommended for UR-PDAC, but the optimal regimen for conversion surgery remains unclear.

The role of adjuvant chemotherapy following conversion surgery is also uncertain. While its efficacy in resectable PDAC is well documented in the JASPAC01 trial [10], evidence in the context of conversion surgery is lacking. Similarly, the use of radiotherapy remains debatable. Surgical intervention for UR-PDAC is typically more invasive than for resectable PDAC, requiring careful consideration of patient condition, choice and timing of adjuvant therapy, and the overall surgical burden. Finally, a major limitation of this study is the absence of validated biological markers to guide the selection of patients most likely to benefit from conversion surgery.

Conclusion

Our findings underscore the importance of multidisciplinary management, including chemoradiotherapy and conversion surgery, in selected patients with UR-PDAC. However, critical questions remain regarding the indications for surgery, optimal chemotherapy regimens, duration of preoperative therapy, and precise criteria for patient selection. Well-designed prospective studies are needed to address these uncertainties and optimize treatment strategies for UR-PDAC patients.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Foundation for Promotion of Cancer Research (FPCR). Cancer Statistics in Japan 2019. Tokyo: FPCR; 2019. Available from: https://www.fpcr.or.jp/data_files/view/41/mode:inline
2. Jonathan DM, Rishi S, Juan WV, Rachna TS. Pancreatic cancer. Lancet. 2020;395(10242):2008–20.
3. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378(9791):607–20.
4. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 1.2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf
5. Japan Pancreas Society. General Rules for the Study of Pancreatic Cancer. 7th ed. Tokyo: Kanehara Shuppan;2016.
6. Imamura M, Doi R, Imaizumi T, Funakoshi A, Wakasugi H, Sunamura M, et al. A randomized multicenter trial comparing resection and radiochemotherapy for resectable locally invasive pancreatic cancer. Surgery. 2004;136(5):1003–11.
7. Hackert T, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, et al. Locally advanced pancreatic cancer: Neoadjuvant therapy with FOLFIRINOX results in resectability in 60% of the patients. Ann Surg. 2016;264(3):457–63.
8. Sui K, Okabayashi T, Shima Y, Morita S, Iwata J, Sumiyoshi T, et al. Clinical effects of chemoradiotherapy in pursuit of optimal treatment of locally advanced unresectable pancreatic cancer. Br J Radiol. 2017;90(1072):20170165.
9. Saito T, Ishido K, Kudo D, Kimura N, Wakiya T, Nakayama Y, et al. Combination therapy with gemcitabine and nab-paclitaxel for locally advanced unresectable pancreatic cancer. Mol Clin Oncol. 2017;6(6):963–7.

10. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: A phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2016;387(10018):248–57.
11. Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX. Ann Surg. 2015;261(1):12–7.
12. Klaiber U, Hackert T. Conversion surgery for pancreatic cancer—The impact of neoadjuvant treatment. Front Oncol. 2020;10(no issue):1501.
13. Satoi S, Yamaue H, Kato K, Takahashi S, Hirono S, Takeda S, et al. Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with long-term favorable response to nonsurgical treatments. J Hepatobiliary Pancreat Sci. 2013;20(6):590–600.
14. Gillen S, Schuster T, Büschenfelde CMZ, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: A systematic review and meta-analysis. PLoS Med. 2010;7(4):e1000267.
15. Yoshitomi H, Takano S, Furukawa K, Takayashiki T, Kuboki S, Ohtsuka M. Conversion surgery for initially unresectable pancreatic cancer: Current status and unsolved issues. Surg Today. 2019;49(10):894–906.
16. Natsume S, Shimizu Y, Senda Y, Hijioka S, Matsuo K, Ito S, et al. Conversion surgery only for highly selected patients with unresectable pancreatic cancer. Surg Today. 2019;49(8):670–7.
17. Furuse J, Shibahara J, Sugiyama M. Development of chemotherapy and significance of conversion surgery after chemotherapy in unresectable pancreatic cancer. J Hepatobiliary Pancreat Sci. 2018;25(4):261–8.
18. Yanagimoto H, Satoi S, Yamamoto T, Yamaki S, Hirooka S, Kotsuka M, et al. Benefits of conversion surgery after multimodal treatment for unresectable pancreatic ductal adenocarcinoma. Cancers (Basel). 2020;12(6):1428.
19. Asano T, Hirano S, Nakamura T, Okamura K, Tsuchikawa T, Noji T, et al. Survival benefit of conversion surgery for patients with initially unresectable pancreatic cancer. J Hepatobiliary Pancreat Sci. 2018;25(5):342–50.
20. Kimura Y, Nakamura T, Hayashi T, Kuwatani M, Motoya M, Yoshida M, et al. Clinical usefulness of conversion surgery for unresectable pancreatic cancer: A multicenter study by HOPS UR-01. Ann Gastroenterol Surg. 2019;3(5):523–33.
21. Tsuchiya N, Matsuyama R, Murakami T, Yabushita Y, Sawada Y, Kumamoto T, et al. Role of conversion surgery for unresectable pancreatic cancer after long-term chemotherapy. World J Surg. 2020;44(8):2752–60.
22. Klaiber U, Schnaidt ES, Hinz U, Gaida MM, Heger U, Hank U, et al. Prognostic factors of survival after neoadjuvant treatment and resection for initially unresectable pancreatic cancer. Ann Surg. 2021;273(1):154–62.
23. Lee J, Lee JC, Gromski MA, Kim HW, Kim J, Kim J, et al. Clinical outcomes of FOLFIRINOX in locally advanced pancreatic cancer: A single center experience. Medicine (Baltimore). 2018;97(34):e13592.
24. Chad AB, Ashley NK, Mohammed A, Callisia NC, Kathleen KC, Abdul HK, et al. Is adjuvant therapy necessary for all patients with localized pancreatic cancer who have received neoadjuvant therapy? J Gastrointest Surg. 2017;21(10):1793–803.
25. Satoi S, Yamamoto T, Yamaki S, Sakaguchi T, Sekimoto M. Surgical indication for and desirable outcomes of conversion surgery in patients with initially unresectable pancreatic ductal adenocarcinoma. Ann Gastroenterol Surg. 2019;4(1):6–13.
26. Yamada S, Kobayashi A, Nakamori S, Baba H, Yamamoto M, Yamaue H, et al. Resection for recurrent pancreatic cancer in the remnant pancreas after pancreatectomy is clinically promising: Results of a project study for pancreatic surgery by the Japanese society of hepato-biliary-pancreatic surgery. Surgery. 2018;164(6):1049–56.
27. Kurahara H, Maemura K, Mataki Y, Tanoue K, Iino S, Kawasaki Y, et al. Lung recurrence and its therapeutic strategy in patients with pancreatic cancer. Pancreatology. 2020;20(1):89–94.
28. Michelakos T, Pergolini I, Castillo CFD, Honselmann KC, Cai L, Deshpande V, et al. Predictors of resectability and survival in patients with borderline and locally advanced pancreatic cancer who underwent neoadjuvant treatment with FOLFIRINOX. Ann Surg. 2019;269(4):733–40.
29. White RR, Xie HB, Gottfried MR, Czito BG, Hurwitz HI, Morse MA, et al. Significance of histological response to preoperative chemoradiotherapy for pancreatic cancer. Ann Surg Oncol. 2005;12(3):214–21.

30. Tanaka M, Heckler M, Mihaljevic A, Sun H, Klaiber U, Heger U, et al. CT response of primary tumor and CA19-9 predict resectability of metastasized pancreatic cancer after FOLFIRINOX. Eur J Surg Oncol. 2019;45(8):1453–9.
31. Moutardier V, Magnin V, Turrini O, Viret F, Hennekinne-Mucci S, Gonçalves A, et al. Assessment of pathologic response after preoperative chemoradiotherapy and surgery in pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys. 2004;60(2):437–43.
32. Chatterjee D, Katz MH, Rashid A, Varadhachary GR, Wolff RA, Wang H, et al. Histologic grading of the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: A predictor for patient outcome. Cancer. 2012;118(12):3182–90.
33. Shinchi H, Maemura K, Mataki Y, Kurahara H, Sakoda M, Ueno S, et al. A phase II study of oral S-1 with concurrent radiotherapy followed by chemotherapy with S-1 alone for locally advanced pancreatic cancer. J Hepatobiliary Pancreat Sci. 2012;19(2):152–8.
34. Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: A phase 2/3 trial. Ann Surg. 2018;268(2):215–22.
35. Hammel P, Huguet F, van Laethem JL, Goldstein D, Glimelius B, Artru P, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer: The LAP07 randomized clinical trial. JAMA. 2016;315(17):1844–53.
36. Kato K, Kondo S, Hirano S, Tanaka E, Shichinohe T, Tsuchikawa T, et al. Adjuvant surgical therapy for patients with initially unresectable pancreatic cancer with long-term favorable responses to chemotherapy. J Hepatobiliary Pancreat Sci. 2011;18(5):712–6.
37. Frigerio I, Regi P, Giardino A, Scopelliti F, Girelli R, Bassi C, et al. Downstaging in stage IV pancreatic cancer: A new population eligible for surgery? Ann Surg Oncol. 2017;24(8):2397–403.
38. Nitsche U, Wenzel P, Siveke JT, Braren R, Holzapfel K, Schlitter AM, et al. Resectability after first-line FOLFIRINOX in initially unresectable locally advanced pancreatic cancer: A single-center experience. Ann Surg Oncol. 2015;22(4):1212–20.