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Clinical Implications of Conversion Surgery for Initially Unresectable, Locally Advanced Pancreatic Adenocarcinoma. A Single Center Experiences

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Abstract

Background: Recent advances in anticancer treatment for unresectable Pancreatic Adenocarcinoma (PDAC) facilitate good disease control, and considering who might benefit from Conversion Surgery (CS) among those with a favorable response to induction treatment remains controversial.

Objectives: The aim of this study was to evaluate patients' outcomes and identify indicators for selecting conversion surgery after multidisciplinary induction treatment for initially unresectable and locally advanced (UR-LA) pancreatic adenocarcinoma.

Methods: Among 727 patients in a hospital-based PDAC database from 1997 to 2016, 93 who were clinically diagnosed as UR-LA on imaging were included in this retrospective cohort. Treatment regimens and overall survival (OS) were analyzed in relation to CS. Univariate and multivariate analyses were undertaken to determine predictors for OS. Prognostic scores, such as the high-sensitivity modified Glasgow prognostic score (HS-mGPS) and the prognostic nutritional index (PNI), were also evaluated.

Results: For the 93 UR-LA PDAC cases, chemotherapy (CT) with or without chemoradiotherapy (CRT) was given as 1st and 2nd line treatment. CS was completed in 15 (16.1%) patients at 10.7 months after induction treatment, with all cases achieving R0. OS was significantly better in the CS group (32.9 *vs.* 15.6 months, p=0.0008). Independent predictors for OS were CS (HR 0.23, 95% CI 0.09-0.63, p=0.004) and pre-treatment HS-mGPS [2-3; HR 1.96, 95% CI 1.09-3.52, p=0.024].

Conclusions: CS following a favorable response to induction therapy for UR-LA PDAC may be a good option to prolong survival. The preoperative HS-mGPS was significantly related to the prognosis of UR-LA PDAC patients.

Keywords: Pancreatic adenocarcinoma; Unresectable; Locally advanced; Radical surgery; Conversion

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Introduction

Pancreatic adenocarcinoma (PDAC) has been ranked as the fourth leading cause of cancer mortality in Western countries [1] and Japan [2]. Despite marked improvements in diagnostic modalities [3,4], the absence of distinctive symptoms and the systemic nature of the disease impair early detection of pancreatic cancer, and more than 80% of cases are diagnosed as unresectable because of its high metastatic potential [5,6]. For non-metastatic PDAC patients with unresectable or borderline resectable tumors, treatment usually involves chemotherapy (CT) and/or radiation in an effort to improve their chance at resectability [7]. Recent advances in anticancer treatment for unresectable or metastatic malignancies facilitate good disease control and patients with those diseases sometimes convert to surgical resection. This surgical strategy is nowadays called "conversion surgery (CS)" [8]. Preceding anticancer treatment and consecutive surgical exploration have been studied so far, but determining who might benefit from conversion surgery among those with a favorable response to induction treatment remains controversial [9-14]. The various

Table 1: Background characteristics of all cohorts.

Factors		UR-LA(n=93)
Gender	M /F	50/ 43
Age		69 [37-89]
PS	0/ 1/ 2/ 3/ 4	52/ 31/ 8/ 1/ 1
ASA	1/ 2/ 3/ 4/ 5	25/ 66/ 1/ 0/ 1
Main tumor location	Ph/ bt	50/ 43
Tumor diameter (mm)		35 [16-76]
UICC-T	3/4	16/ 77
UICC-N	0/ 1	77/ 16
UICC-stage	IIA/IIB/III	12/3/1978
Unresectable factor (dominant)	CHA	17
	CA	26
	SMA	44
	PV	6
Pathological proof	Adenocarcinoma	74
	Atypical epithelium	10
	Undetermined	9
Pre-treatment CA19-9 (U/ml)		383 [7.9-71940]
Follow-up period (months)*		14 [1-75]

*for censored cases

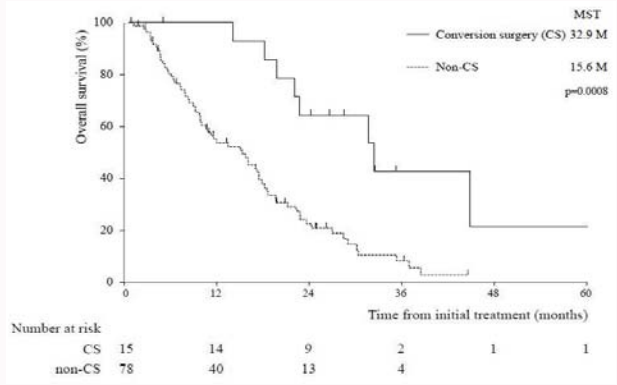

Figure 1: Kaplan-Meier plots for overall survival by conversion surgery (CS). The mark [|] denotes a censored case.
Median survival time: MST.

regimens and approaches each have their limitations, and most have imperfect success.

This study aimed to evaluate patients' outcomes and identify indicators for selecting conversion surgery after multidisciplinary induction treatment for initially unresectable and locally advanced (UR-LA) PDAC in a single, middle-volume center.

Patients and Methods

An institutional comprehensive database search identified 727 PDAC patients between January 1994 and November 2016. The following categories were excluded from the present investigation: resectable disease (n=202); borderline resectable disease (n=102); unresectable-metastatic (n=304) according to NCCN resectability criteria [7]; and unknown details (n=19). A final total of 93 patients clinically diagnosed with UR-LA were included in this retrospective cohort. Clinical data of all patients were obtained from medical records. Gender, age at the time of diagnosis, Performance Status (PS), American Society of Anesthesiologists physical Status Classification (ASA), levels of CRP, serum albumin, and lymphocyte counts before initial treatment were retrospectively reviewed. Multimodal image findings such as multi-detector row computed tomography, contrast-enhanced ultrasonography, and gadoxetic acid-enhanced magnetic resonance imaging were usually undertaken to stage diseases adequately. Definitions of resectability were based on NCCN version 2 in 2012 [7]. In brief, celiac abutment of pancreatic head cancer or arterial encasement more than half of the circumference in other situations was categorized as Unresectable (UR), and we certainly confirmed that all patients had URLA-PDAC initially. Regarding the Common Hepatic Artery (CHA), URLA diagnosis was adapted when safe and complete resection and reconstruction were very difficult because of the tumor extension to the bifurcation of the hepatic artery. Pathological proof of pancreatic ductal adenocarcinoma was basically obtained by endoscopic ultrasound-guided fine-needle aspiration or brushing-cytology during endoscopic retrograde cholangiopancreatography. The outcome measures included preceding treatment regimen, the rate of conversion to radical surgeries, Overall Survival (OS) by conversion surgery, and predictors for conversion or OS. Prognostic scores were also evaluated to determine predictors for conversion or OS. The high-sensitivity modified Glasgow prognostic score (HS-mGPS) was calculated as follows: CRP ≤ 0.3 mg/dl and albumin ≥3.8 g/dl=0; albumin <3.8 g/dl=1; CRP >0.3 mg/dl=2; and CRP > 0.3 mg/dl and albumin <3.8 g/dl=3 [15]. The prognostic nutritional index, PNI [16], was calculated as (10 × albumin) + (0.005 × lymphocyte count). HS-mGPS and PNI were evaluated in 87 patients whose detailed data were available.

Conversion Surgery (CS) was indicated in patients who maintained Partial Response (PR) or Stable Disease (SD) according to the RECIST criteria [17] for more than 6 months, in which levels of tumor markers or the positron emission tomography-standard uptake value (PET-SUV) decreased adequately, and with proper disease control that would allow an attempt at radical surgery. The histologic assessment of the extent of preceding treatment response was evaluated by the Evans' grading system [18]. The Clavien-Dindo (C.D.) classification was applied to postoperative complications [19]. Mortality was defined as death within hospital stay after surgery.

Statistical analysis

Comparisons between two groups were carried out using the χ^2 test and the Mann-Whitney U test or Cox proportional hazard regression modeling for nonparametric data. Factors found to be significant or with values of $p \leq 0.2$ on univariate analysis without potential confounding were subjected to multivariate logistic regression analysis to determine adjusted odds ratios. OS was calculated using Kaplan-Meier methods with the log-rank test. All calculations were done with Stat Mate V (ATMS Co., Ltd., Tokyo, Japan), or SPSS version 16.0 (SPSS, Chicago, IL). All continuous values are expressed as medians [range]. Values of $P<0.05$ were considered significant.

Results

Patient characteristics

The background characteristics of the patients are summarized in Table 1. The patients included 50 men and 43 women, with a mean age of 69 years at the time of diagnosis (range, 37 years to 89 years). Entire patients were of performance status (PS) 0-1 and American Society of Anesthesiologists physical status classification (ASA) 1-2. Regarding the primary tumor location and its diameter on imaging diagnosis, 50 patients had tumor in the pancreatic head

Table 2: Lines and regimens of treatment within 2nd line.

No. of lines	Lines	Regimens	All cohort (n=93)	Non-surgery (n=78)	Surgery (n=15)	p-value
1st-line	CRT		32	22	10	0.2167
	CT		37	33	4	
	AI		13	12	1	
	Vac		3	3	0	
	CT regimen	GEM	17	16	1	0.2181
		S1	10	10	0	
		GS	3	3	0	
		FFX	6	3	3	
		GnP	1	1	0	
2nd-line	CRT		12	7	5	0.4535
	CT		45	35	10	
	AI		1	1	0	
	Vac		1	1	0	
	CT regimen	GEM	21	18	3	0.0968
		S1	14	12	2	
		GS	7	2	5	
		FFX	2	2	0	
		GnP	1	1	0	

CRT: Chemoradiotherapy; CT: Chemotherapy; AI: Arterial Infusion Chemotherapy; Vac: Cancer Vaccine Therapy; GEM: Gemcitabine; FFX: FOLFIRINOX; GnP: Gemcitabine Plus Nab-Paclitaxel; GS: Gemcitabine Plus S

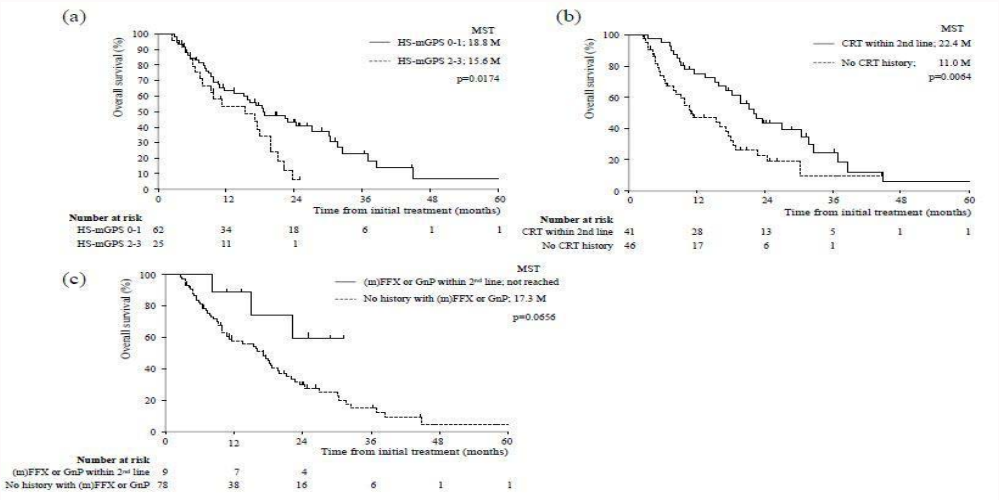

Figure 2: Kaplan-Meier plots for overall survival by subgroups; the HS-mGPS 0-1 vs. 2-3 (a); chemoradiotherapy within 2nd-line treatment yes vs. no (b); with or without (modified) FOLFIRINOX or gemcitabine plus nab-Paclitaxel within 2nd-line treatment (c). The mark [|] denotes a censored case. Median survival time: MST.

region and 43 in the pancreatic body-tail regions. Clinical UICC-T status were compatible with locally advanced diseases status and regional lymphnode metastasis was suspected in 16 patients, so that clinical UICC-stage resulted in IIA with 12, IIB with 3 and III with 78 patients. Among factors dominantly causing unresectability, tumor contact with Superior Mesenteric Artery (SMA) was most frequent in 44 patients, Celiac Axis (CA) in 26 patients, common hepatic artery (CHA) in 17 patients, and portal vein (PV) in 6 patients. The pathological proof was established for adenocarcinoma in 74 patients (79.6%), for suspicious of adenocarcinoma in 10 patients (10.8%) and undetermined or not implemented in 9 patients (9.6%). The median follow-up period for censored cases was 14 months.

Preceding anticancer treatment

Lines and regimens of treatment within 2nd line are summarized in Table 2. Of the 93 UR-LA PDAC cases, chemoradiotherapy (CRT), CT, and other treatments were given to 32, 37, and 16 patients as 1st-line treatment, and to 12, 45, and 2 patients as 2nd-line treatment, respectively. CT regimens comprised gemcitabine, S1, gemcitabine plus S1, (modified) FOLFIRINOX, and Gemcitabine plus Nab-paclitaxel (GnP) in 17, 10, 3, 6, and 1 patient in 1st-line and 21, 14, 7, 2 and 1 patient in 2nd-line treatment, respectively. In all cohorts, CRT and systemic CT were mainly adopted in 1st-line, followed by systemic CT as 2nd-line treatment. In the chemotherapeutic regimens, gemcitabine or S1 monotherapy and gemcitabine plus

Table 3: Summary of the patients with conversion surgery.

Factors		Surgery (n=15)
Gender	M/F	9/6
Age		66 [46-76]
Interval from initial treatment (months)		10.7 [4.7-61.4]
Operation procedures		
Pancreaticoduodenectomy		8
Combined vascular resection	PV-SMV	4
	PV-SMV+HAR	2
	PV-SMV+CA-HA-SpA	1
Distal pancreatectomy		7
Combined vascular resection	CA	3
	CA+PV-SMV	3
Laparoscopic/open		1/14
Operative time (min)		568 [342-1035]
Operative blood loss (ml)		275 [70-2240]
Intraoperative transfusion (U)		0 [0-10]
Surgical morbidities	(C.D. ≥IIIa)	7 (46.7%)
Surgical mortality	(C.D.=V)	0
Pathological findings		
UICC-pT	0/ 1/ 3	3/3/9
UICC-pN	0/ 1	12/3
UICC-Stage	pCR/ IA/ IIA/ IIB	3/ 2/ 7/ 3
R	0	15 (100%)
Evans grade	I/ IIa	2/3
	IIb/ III/ IV	5/2/3
Adjuvant treatment	Yes/No	12 (80%)/3
Initiation of adjuvant treatment (months)		2.8 [0.3-9.1]

R: Residual Tumor; POD: Postoperative Days; SD: Standard Deviation; C.D: Clavien-Dindo Classification; PV-SMV: Portal and Superior Mesenteric Vein; HAR: Hepatic Artery Resection; CA: Celiac Artery; SpA: Splenic Artery

S1 covered 80% of patients in the 1st-line regimen and 93% in the 2nd-line regimen. There was no bias in selection of treatment lines and CT regimens. Regarding chemotherapeutic regimens according to the lines of treatment, gemcitabine or S1 monotherapy was the mainstream treatment, because the median date for initiating 1st-line treatment was 2011, which was before the era of FOLFIRINOX and gemcitabine plus Nab-paclitaxel in Japan.

Surgical conversion and outcomes

Radical surgery was attempted for 16 patients after 3rd-line treatment, and it was completed in 15 patients (9 men and 6 women; median age 66 years). Based on the results of examinations so far, the conversion rate to surgery was 16.1% in this retrospective cohort. The perioperative data in patients with radical surgery are summarized in Table 3. The operative procedures included pancreaticoduodenectomies in 8 patients and distal pancreatectomies in 7 patients at a median interval of 10.7 months after the induction treatment (Table 3). When comparing treatment lines and regimens by surgery up to 2nd line, there was no significant difference between these two groups (Table 2). Concomitant vascular resections were performed in 13 of 15 patients, and the details were CHA in 2, celiac axis (CA) in 6, CHA-CA-splenic artery (SpA) in 1, and portal-superior mesenteric vein in 10. Six patients required combined arterial and portal resection. These procedures took 568 mins, and the median estimated blood loss during surgery was 275 ml. The surgical morbidities and mortality were 46.7% and 0%, respectively, although extended radical surgery with vascular resection was performed in 86.7% of surgical cases. Pathological findings were pT1 in 3 patients and pT3 in 9 patients. Nodal status was negative in 12 cases. Three cases were diagnosed as pathological complete response, and 2 cases were final stage IA, so that 5 of 12 cases were down-staged. All cases achieved R0, and pathological tumor responses exceeding Evans grade IIb were seen in 10 of the 15 cases. Adjuvant CT was given to 80% of patients, with a median interval of 2.8 months (range, 0.3-9.1).

Table 4: Details in 12 patients with postoperative recurrence.

Site of initial recurrence (n=12)	n	%	Period from CS to relapse: months: median (range)
Peritoneum	5$	41.7%	5.9 (2.5 - 12.7)
Liver	4#	33.3%	6.1 (4.1 - 10.7)
Remnant pancreas	1#	8.3%	4.1
Locoregional	1$	8.3%	9.3
Pleura	1	8.3%	8.4
Ureter	1	8.3%	13.5
Bone	1	8.3%	15.9
Period from CS to relapse: months: median (range)			9.1 (2.5 - 15.9)
Period from initial treatment to relapse: months: median (range)			20.9 (12.8 - 70.7)
CS: coversion surgery			

$ #: Initial recurrence was found at dual sites in two patients

Oncological outcome

Recurrence was initially confirmed in 12 (14 sites) of 15 patients (75.0%) (Table 4). Five patients had peritoneal dissemination, four had liver metastasis and each one had lung, remnant pancreas, right pleura, left ureter and bone metastasis. The median duration from CS or initial treatment to recurrence was 9.1 (range, 2.5-15.9) or 20.9 (12.8-70.7) months, respectively. Besides, we considered the time to relapse by the recurrence site. The median time to peritoneal dissemination was 5.9 (range, 2.5-12.7) months and liver metastasis was 6.1 (range, 4.1-10.7) months.

OS from initial treatment was compared with and without conversion surgery, and there was a significant difference between the two groups (Figure 1). The Median Survival Time (MST) of patients with conversion surgery was 32.9 months, which was significantly longer than in the non-conversion group, at 15.6 months (log-rank p=0.0008).

Significant predictor for surgical conversion and overall survival

To determine significant predictors for conversion or OS, prognostic scores, such as the pre-treatment HS-mGPS and PNI, were also evaluated in 87 patients for whom detailed data were available. The background characteristics of patients with or without conversion surgery are summarized in Table 5, and gender, age, PS, ASA, PNI, HS-mGPS, and initial stage of disease were generally comparable. In the treatment history, the surgery group was more likely to have had CRT within 2nd line, and such modern chemotherapeutic regimens as FOLFIRINOX or Gemcitabine plus Nab-Paclitaxel were evenly used in the two groups (Table 5). Of the various clinicopathological parameters, age over 70 years (HR 0.308, 95% CI 0.09-1.06, p=0.061), UICC cN1 (HR 4.00, 95% CI 1.09-14.7,

Table 5: Background characteristics of patients with or without conversion surgery.

Factors		Non-surgery (n=72)	Surgery (n=15)	*p*-value
Gender	Male/ Female	37/ 35	9/6	0.7463
Age	median [range]	71 [37-89]	66 [46-76]	0.152
Performance status	0	39	10	0.3746
	1-4	33	5	
ASA	1	20	4	0.8182
	2-5	52	11	
CRP		0.10 [0.10-5.50]	0.14 [0.10-2.12]	0.8607
Alubumin		4.1 [2.4-4.9]	4.0 [2.9-4.6]	0.651
Lymphcyte count		1323 [440-2632]	1350 [141-2574]	0.9462
PNI	median [range]	47 [29-61]	47 [34-51]	0.883
HS-mGPS	0-1	52	11	0.8182
	2-3	20	4	
Tumor location	Ph/bt	38/ 34	8/7	0.8064
Tumor diameter (mm)	median [range]	34[16-66]	36 [19-76]	0.8528
UICC-T	3	10	4	0.4015
	4	62	11	
UICC-N (0 vs. 1)	0	64	10	0.0722
	1	8	5	
CA 19-9 (U/ml)	median [range]	392 [8-15696]	390 [52-71940]	0.8607
Treatment history				
CRT within 2nd line	Yes/ No	26/ 46	15/ 0	0
(m)FFX or GnP within 2nd line	Yes/ No	6/66	3/12	0.0947

ASA: American Society of Anaesthesiologists Physical Status Classification; PNI: Prognostic nutritional index; HS-mGPS: High Sensitive-Modified Glasgow Prognostic Score; CRT: Chemoradiotherapy; (m)FFX: (modified) FOLFIRINX; GnP: Gemcitabine Plus Nab-Paclitaxel

p=0.037), initial levels of CA 19-9 over the median value of 123 U/ml (HR 3.25, 95% CI 0.68-15.58, *p*=0.140), and treatment history of modern chemotherapeutic regimens within 2nd-line (HR 2.750, 95% CI 0.60-12.52, *p*=0.191), with p-values less than 0.2 on univariate analysis, were included in multiple regression analyses, but none was identified as a significant predictor of conversion (data not shown). Next, the prognostic factors related to OS were analyzed (Table 6). PS (≥ 1), HS-mGPS (≥ 2), treatment history of CRT, FOLFIRINOX or Gemcitabine plus Nab-Paclitaxel within 2nd line, and conversion surgery had p-values less than 0.2 on univariate analysis, and they were included in the multivariate analyses with a Cox proportional hazard model. HS-mGPS (2-3; HR 1.96, 95% CI 1.09-3.52, *p*=0.024) and conversion surgery (HR 0.23, 95% CI 0.09-0.63, *p*=0.004) were significant predictors of OS (Table 6). The subgroup analyses showed that the survivals of patients with HS-mGPS ≤ 1 (MST 18.8 M *vs.* 15.6 M, log-rank *p*=0.0174) and CRT within 2nd line treatment (MST 22.4 M *vs.* 11.0 M, log-rank *p*=0.0064) were significantly better than the others. Such modern chemotherapeutic regimens as FOLFIRINOX or Gemcitabine plus Nab- Paclitaxel within 2nd line had a marginal tendency for better patients' survival (MST not reached *vs.* 17.3 M, log-rank *p*=0.0656) (Figure 2).

Discussion

This retrospective cohort study demonstrated that overall survival of patients who underwent conversion surgery after successful multidisciplinary induction treatment in initially unresectable, locally advanced (UR-LA) pancreatic adenocarcinoma was significantly longer compared to those who did not, and that the prognostic factors for pre-treatment UR-LA PDAC patients was HS-mGPS 0 to 1 with low tumor-related inflammation status. Recent management of PDAC has gradually advanced, such as resectability status based on vascular involvement assessed by preoperative imaging (resectable, borderline resectable, and locally advanced disease) [7], and the availability of more effective chemotherapeutic regimens including FOLFIRINOX and Gemcitabine plus nab-Paclitaxel [20,21]. Unfortunately, the majority of patients with PDAC present with metastatic or UR-LA tumors, and more aggressive multimodality treatments have been used for the management of such staged disease [12,13]. In the most recent meta-analysis based on reports since 2009, the conversion rate of UR-LA to surgery with an Intention-To-Treat (ITT) analysis was reported to be 26%, and the OS was 18.7 M [13]. Theoretically, the neoadjuvant treatment approach downstages nodal disease and vascular abutment, increases the rate of margin-negative resection, and also helps identify patients at risk of early disease progression [22,23]. The conversion rate of 16.1% in the present study seemed to be lower than recent report [12], and is thought to be due to the facts that the median year for the start of treatment was 2011, and the percentage of patients who received 1st line treatment with FOLFIRINOX or Gemcitabine plus nab-Paclitaxel was less than 10%.

Hackert, on the other hand, recently reported that locally advanced pancreatic cancer was successfully treated with neoadjuvant FOLFIRINOX that resulted in resectability in 60% of the patients [14], although this cohort included borderline-resectable disease. Other meta-analysis addressing the treatment result of FOLFIRINOX to initially unresectable PDAC reported the rate of completing radical surgery and R0 as 28% (0% to 43%) and 74%, respectively [12]. The OS of 32.9 M in the present study is thought to be attributable to the

Table 6: Univariate and multivariate analyses of factors predictive of overall survival.

Factors		Univariate				Multivariate			
		p-value	HR	95%	CI	*p*-value	HR	95% CI	CI
Gender	Female	0.58	0.87	0.519	1.444				
Age	≥70 y.o.	0.632	1.13	0.681	1.881				
Performance status	≥1	0.119	1.5	0.901	2.492	0.239	1.43	0.79	2.57
ASA	≥2	0.356	0.77	0.44	1.343				
Onodera PNI	≥41	0.558	0.71	0.218	2.274				
HSmGPS score	≥2	0.02	1.96	1.114	3.458	0.024	1.96	1.09	3.52
Tumor diameter	≥36mm	0.67	1.12	0.671	1.859				
UICC-T (3 vs. 4)	4	0.743	0.89	0.432	1.82				
UICC-N (0 vs. 1)	1	0.712	0.88	0.441	1.75				
Tumor marker	CA19-9 ≥123.3	0.497	0.82	0.468	1.446				
	CA19-9 ≥500	0.8	1.07	0.637	1.795				
	CA19-9 ≥1000	0.437	0.79	0.445	1.419				
Treatment history	CRT within 2nd line	0.008	0.49	0.288	0.826	0.842	0.94	0.5	1.76
	(m)FFX or GnP within 2nd line	0.079	0.35	0.11	1.127	0.319	0.55	0.17	1.79
Conversion surgery	yes	0.001	0.2	0.079	0.504	0.004	0.23	0.09	0.63

ASA: American Society of Anaesthesiologists Physical Status Classification; PNI: Prognostic Nutritional Index; HS-mGPS: High Sensitive-Modified Glasgow Prognostic Score; CRT: Chemoradiotherapy; (m)FFX: (modified) FOLFIRINX; GnP: Gemcitabine Plus Nab-Paclitaxel; Med: Median

facts that the preoperative multimodal treatment was performed for the relatively long period of 10 months or more, and that R0 resection was achieved in all cases.

No consensus has been reached with regard to the timing of conversion to radical surgery after induction therapy or the duration of 1st line treatment for UR-LA PDAC. In a retrospective cohort study with a middle-sized sample, OS was good in patients who received preoperative treatment over a long period, with reported treatment durations of ≥ 20 weeks [22] and 8 months or 12 months or more [10]. In the present study, the median preoperative treatment period was 10.7 months, and the mean was 14.5 months. Although this was generally consistent with past reports, the number of patients was small, and so an investigation by treatment duration could not be done. In general, the prognosis with malignant tumors is affected greatly by the nutritional status of the individual and the extent of tumor-associated inflammation [15]. In pancreatic cancer as well, the lymphocyte count [16] and Glasgow Prognostic Score [24] have been shown to correlate strongly with prognosis in patients with resectable PDAC. At the same time, no studies have analyzed the pretreatment prognostic score of UR-LA PDAC, making the present study the first to do so.

Pretreatment HS-mGPS was independent prognostic factor for the survival period after the start of initial anticancer treatment in the present study, although that had no correlation with surgical conversion according to the success of preoperative treatment. The subgroup analyses also demonstrated that preceding anticancer treatment with CRT or modern chemotherapeutic regimens including FOLFIRINOX or Gemcitabine plus Nab-paclitaxel might offer better oncological outcomes than conventional anticancer regimens. Whether to administer radiation or a modern regimen preoperatively, however, remains controversial in the management of locally advanced pancreatic adenocarcinoma today [25-29]. All patients converted to radical surgery in this retrospective cohort had completed CRT preoperatively, and this may have had a strong effect on the better outcomes of these patients. The number and observational periods of patients who underwent preoperative FOLFIRINOX or Gemcitabine plus Nab-paclitaxel treatment were too small and too short to conclude that those regimens were superior.

There are of course limitations in this study, including that it was a retrospective study that it was a study with a small number of patients in a single institution, and that nutritional status and the extent of tumor-associated inflammation were only assessed before induction treatment. The inconsistency in decision-making with regard to indications for surgery and decisions made based on the inclinations of the attending physician in each case were major reasons why an analysis of the best timing for surgical conversion could not be done. The predictors for conversion were not determined, perhaps because the series of treatments was not determined systematically, but was based on the attending physician, which greatly affected these results. In our hospital, decision-making has been largely standardized based on multimodal treatment conferences since 2012. The HS-mGPS and PNI are known to affect oncological outcomes [15,16,24]; however, the rate of change of these values during preoperative treatment might be more important. The increase or decrease of these indices could not be evaluated in this study because a complete data set was not available.

Recent advancements in anticancer treatment for unresectable or metastatic PDAC facilitate good disease control. Since induction treatment with FOLFIRINOX [27] or Gemcitabine plus Nab-paclitaxel [30] has a higher response rate than conventional treatment, the question of who might benefit from conversion surgery among those with a favorable response to induction treatment needs to be carefully considered in the near future. In our retrospective cohort study, the prognostic factors for pre-treatment UR-LA patients was HS-mGPS 0 to 1 with low tumor-related inflammation status, and surgical conversion significantly prolonged patients' survival.

Conclusion

Conversion surgery following a favorable response to induction treatment for UR-LA PDAC may be a good option to prolong patient

survival. The HS-mGPS was strongly correlated with the prognosis of UR-LA PDAC patients for whom multidisciplinary induction therapy was planned. A further prospective study with a larger sample size is warranted to evaluate the ideal induction treatment regimen or the timing for radical surgery.

Author's Contributions

Kimura and Imamura had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kimura, Imamura, Yamaguchi, Motoya and Yoshida. Acquisition or interpretation of data: Kimura, Imamura, Yamaguchi, Motoya and Yoshida. Draft of the manuscript: Kimura, Yamaguchi, Takemasa. Critical revision of the manuscript for important intellectual content: Kimura, Nakase, Sakata, Kato and Takemasa. Administrative, technical, or material support: Kimura, Mizuguchi, Hirokawa, Nagayama and Takemasa. Study supervision: Takemasa.

Compliance with Ethical Standards

This retrospective study was approved by the ethics committee of Sapporo Medical University Hospital (292-23). The applicable law and ethical principles pertaining to the protection of human subjects provide for waiver of consent from a research ethics committee for a retrospective study of this type.

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