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ORIGINAL ARTICLE

Conversion surgery only for highly selected patients with unresectable pancreatic cancer: a satisfactory outcome in exchange for a lower resection rate

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Abstract

Purpose The purpose of this study is to clarify the resection rate, safety, and significance of conversion surgery for highly selected patients with unresectable pancreatic cancer (URPca).

Methods We studied 434 URPca patients. Conversion surgery was permitted only for patients who met following requirements: responders to first-line therapy, showing sufficient reduction of the local tumor to enable complete resection, at least 6 months of disease control, and no metastatic lesions detected on radiological examinations (for patients with metastatic disease). The overall survival (OS) was compared between patients who underwent surgery and those who did not. Furthermore, a multivariate analysis was performed to identify possible predictive factors for both total patients with URPca and responders.

Results Conversion surgery was performed in 18 patients (4.1%). The pathologically complete resection rate was 88.9% (16/18). The median operative time, blood loss, and hospitalization duration were 450 min, 780 ml, and 29 days, respectively. The OS was significantly better in patients who underwent surgery than in those who did not. In a multivariate analysis, conversion surgery was shown to be significantly correlated with the OS both in total patients and responders.

Conclusions A satisfactory outcome was achieved for highly selected patients with URPca in exchange for a lower resection rate (4.1%).

Keywords Unresectable pancreatic cancer · Conversion surgery · Resection rate

Introduction

Although pancreatic cancer continues to be a highly lethal disease, the prognosis of patients with resectable cancer has been improving in association with advances in pre- and/or postoperative adjuvant therapy [1, 2]. However, the prognosis of patients diagnosed with unresectable pancreatic cancer (URPca) remains poor, even after the introduction of new anticancer regimens, such as the combination of nab-paclitaxel and gemcitabine (Gnp) and of oxaliplatin, 5-fluorouracil, leucovorin, and irinotecan (FOLFIRINOX), which are known to have strong anticancer effects [3, 4].

Recently, a number of reports have been published regarding an aggressive strategy of performing 'adjuvant surgery' for patients with URPca, mostly for those with unresectable locally advanced (URLA), after 'neoadjuvant therapy' [5–13, 23]. However, these reports may have two unsolved problems. First, the real resection rate for whole URPca patients is still unclear. Although the reported resection rate in previous studies tended to be high (range 13.3–50.8%), those values were calculated using the limited cohort of patients who had been considered to be suitable for future surgery (not the total cohort of URPca patients)

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as a denominator. In addition, the indication of surgery for URPca tended to be inconsistent among studies. Second, whether or not such an aggressive strategy really prolongs the survival of patients with URPca is unclear, as the reported median survival time (MST) of locally advanced disease after the diagnosis has only been around 20 months in previous representative studies [5, 6].

We basically have not considered patients with URPca as candidates for surgery and have performed 'conversion surgery' (not 'adjuvant surgery') only for a very limited pool of patients who met the strict and consistent requirements. The purpose of this study was to clarify the actual resection rate, safety, and significance of conversion surgery for highly select patients with URPca.

Methods

Patients

A total of 434 consecutive patients with URPca (diagnosed according to the criteria defining resectability status in the General Rules for the Study of Pancreatic Cancer, the 7th edition, Japan Pancreas Society [14]) were studied. Regarding the unresectability status, 324 (74.7%) patients were classified as having metastatic (URM) pancreatic cancer, while the remaining 110 (25.3%) were classified as having URLA pancreatic cancer. Regarding the first-line therapy, gemcitabine monotherapy was used in 180 (41.5%); Gnp was used in 124 (28.6%); other gemcitabine-based regimens, such as gemcitabine/erlotinib and gemcitabine/S-1 combinations, were used in 59 (13.6%); FOLFIRINOX was used in 45 (10.4%); S-1 monotherapy was used in 17 (3.9%); and chemoradiation with S-1 was performed in 9 (2.1%) patients. These findings indicate that new anticancer regimens (Gnp or FOLFIRINOX) were used in 169 (38.9%) patients, while conventional regimens (other than Gnp and FOLFIRINOX) were used in 265 (61.1%) patients.

Conversion surgery

The indication of conversion surgery for individual patients was decided at a multidisciplinary conference of pancreatic surgeons, medical oncologists, and radiologists. Among patients who responded (showed a partial or complete response) to first-line therapy according to the guidelines of the Response Evaluation Criteria in Solid Tumors (RECIST) [15], conversion surgery was permitted only for those who met the following requirements: responders to first-line therapy, showing sufficient reduction of the local tumor to enable complete resection, at least 6 months of disease control, and no metastatic lesions detected on radiological examinations (for patients with metastatic disease). For local resection, we are prepared to perform concomitant resection and reconstruction of the hepatic artery to achieve R0 resection. However, we do not perform resection and reconstruction of the superior mesenteric artery. Regarding patient-related factors, we perform conversion surgery according to the same indications for typical pancreatectomy without preoperative treatment, as there is little specific evidence concerning the safety and indications of conversion surgery.

The assessment of outcomes

The Clavien–Dindo (C–D) classification was applied to postoperative complications [16]. Postoperative pancreatic fistula (POPF) was assessed according to the International Study Group of Pancreatic Surgery (ISGPS) definition [17]. The value of CA19-9 was recorded at two points in time: CA19-9 (1), the value at the treatment initiation; and CA19-9 (2), minimum value during first-line therapy. The CA19-9-lowering rate (CA19-9-LR) was calculated as [CA19-9 (1) − CA19-9 (2)]/CA19-9 (1). The size of the primary tumor was measured using an axial image of computed tomography. It was also recorded at two points in time: tumor size (1), the tumor size at the treatment initiation; tumor size (2), the minimum tumor size during first-line therapy. The tumor size-LR (tumor size-LR) was calculated as [tumor size (1) − tumor size (2)]/tumor size (1).

The OS from treatment initiation was compared between patients with and without conversion surgery as well as between patients with and without conversion surgery when the cohort was limited to responder patients. Univariable and multivariable Cox proportional hazard models were used to explore the possible predictive factors for the OS both in the total cohort and in responders. Factors evaluated in the model were conversion surgery (yes vs. no), first-line therapy (new vs. conventional regimen), performance status (0 vs. 1 or 2), sex (male vs. female), tumor location (head vs. body or tail), and unresectability status (URLA vs. URM) as categorical variables and the age, value of serum albumin, log10(CA19-9 (1)), log10(tumor size (1)), CA19-9-LR, and tumor size-LR as continuous variables.

All patient data were collected retrospectively from paper or digitized medical records. This study was approved by the Ethics Review Committee of our center (2017-1-152).

Statistical analyses

We evaluated the impact of conversion surgery on the OS. We defined the OS as the duration between initial treatment and death or the most recent follow-up. To avoid lead-time bias, we treated conversion surgery as a time-varying covariate. The survival rate was calculated using the Kaplan–Meier method, and differences in the survival according to the performance of conversion surgery were evaluated using the log-rank test. The chi-squared test or Fisher's exact probability test was performed for categorical variables. The Mann–Whitney *U* test was applied for the comparison of continuous variables. A *p* value < 0.05 was considered statistically significant. Statistical analyses were performed with the SPSS version 21.0 software program (IBM, Armonk, NY, USA) or Stata version 14.2 (Stata Corp., College Station, TX, USA).

Results

Clinical characteristics of 18 patients who underwent conversion surgery (Table 1)

Conversion surgery was performed in 18 patients (18/434 = 4.1%, URLA, $n = 8$; URM, $n = 10$). Among 10 patients with URM, the histological confirmation of metastatic lesions was obtained in 5 patients (liver: $n = 3$, peritoneum: $n = 2$; cases 9, 10, 13, 15, and 17) at the time of the diagnosis, while it failed to be obtained in the remaining 5 patients (liver: $n = 2$, para-aortic lymph node: $n = 2$, peritoneum: $n = 1$; cases 11, 12, 14, 16, and 18). Instead, distant metastasis was diagnosed with positron emission tomography (PET) or magnetic resonance imaging (MRI) in 4 patients (cases 12, 14, 16, and 18). In case 11, para-aortic lymph node metastasis was diagnosed only with enhanced computed tomography (CT). In this patient, the markedly enlarged lymph node that had been detected at the time of the diagnosis was shown to have disappeared after chemotherapy.

Patients treated with new anticancer regimens (Gnp or FOLFIRINOX) had significantly higher resection rates than those treated with conventional regimens (other than Gnp and FOLFIRINOX) (14/169 = 8.3% vs. 4/265 = 1.5%, respectively, $p = 0.001$). The median time from initial treatment to conversion surgery was 236 days (range 111–614 days). Two patients (cases 3 and 7) underwent conversion surgery as a result of their strong desire for surgery at an early period (111 and 123 days after initial treatment). The treatment response to first-line therapy was PR (partial response) in all patients. The CA19-9 level at the time of conversion surgery was significantly lower than that at the time of the diagnosis [median, 245.1 U/mL (range 0.1–4780.0 U/mL) vs. 23.8 (range 0.1–86.5), $p < 0.001$].

Table 1 Clinical characteristics of 18 patients who underwent conversion surgery (upper half: URLA, lower half: URM)

Case	Sex	Age (year)	Location (Ph/Dp)	UR status (URLA/URM)	Meta organs	First line therapy	Duration (days)[a]	Treatment effect (RECIST)	CA19-9 (1) (U/ml)	CA19-9 (surgery) (U/ml)
1	M	66	Dp	URLA	–	GEM + erlotinib	264	PR	3540.0	62.4
2	F	70	Ph	URLA	–	CRT	284	PR	1684.0	159.3
3	M	57	Dp	URLA	–	Gnp	111	PR	120.2	9.2
4	F	69	Dp	URLA	–	Gnp	325	PR	1199.0	8.4
5	F	47	Ph	URLA	–	Gnp	227	PR	43.3	10.9
6	F	68	Dp	URLA	–	Gnp	161	PR	110.0	45.3
7	F	66	Ph	URLA	–	Gnp	123	PR	2053.0	32.1
8	F	71	Dp	URLA	–	Gnp	379	PR	2561.0	86.5
9	M	71	Dp	URM	Per	GEM	614	PR	204.1	77.3
10	F	73	Dp	URM	Liv	GEM	244	PR	59.2	25.5
11	F	45	Dp	URM	Lnd	FFX	194	PR	10.9	0.1
12	F	58	Dp	URM	Lnd	Gnp	208	PR	169.0	29.1
13	F	61	Ph	URM	Liv	FFX	194	PR	170.6	22.0
14	M	65	Dp	URM	Per	Gnp	190	PR	1018.0	41.5
15	M	72	Dp	URM	Liv	Gnp	256	PR	211.4	51.8
16	F	50	Ph	URM	Liv	FFX	299	PR	3.0	0.1
17	M	69	Dp	URM	Per	Gnp	474	PR	4780	47.4
18	M	62	Ph	URM	Liv	Gnp	183	PR	0.1	0.1

Ph pancreatic head, *Dp* distal pancreas, *UR* unresectability, *URLA* unresectable locally advanced, *URM* unresectable metastatic, *Meta* metastatic, *RECIST* response evaluation criteria in solid tumors, *CA19-9 (1)* value of CA19-9 before treatment, *M* male, *F* female, *Per* peritoneum, *GEM* gemcitabine, *CRT* chemoradiotherapy, *Liv* liver, *Lnd* lymph node, *Gnp* Gem + nab-paclitaxel, *FFX* FOLFIRINOX, *PR* partial response

[a]Duration between treatment initiation and conversion surgery

Outcomes of 18 patients who underwent conversion surgery (Table 2)

Distal pancreatectomy with en bloc celiac axis resection was performed in six patients, distal pancreatectomy in six patients, and pancreaticoduodenectomy in six patients. The median operative time and volume of blood loss were 450 min (range 258–627 min) and 780 mL (range 165–2450 mL), respectively. Postoperative complications developed in 16 (88.9%) patients. Among them, minor complications (C–D class 1 or 2) occurred in 8 (44.4%) patients (delayed gastric emptying: $n = 4$, biochemical leak from pancreatic anastomosis: $n = 2$, enterocolitis: $n = 1$, lymphorrhea: $n = 1$). Major complications (C–D class 3a) occurred in the remaining 8 patients (44.4%) with POPF grade B. There were no perioperative deaths.

The median length of hospitalization was 29 days (range 13–116 days). The R0 resection rate was 88.9% (16/18). Regarding the pathological treatment effect according to the Evans classification [18], grade 1 was achieved in 1 patient (5.6%), grade 2a in 8 (44.4%), 2b in 5 (27.8%), 3 in 2 (11.1%), and 4 in 2 (11.1%). In two patients who underwent hepatectomy combined with pancreatectomy, there were no residual cancer cells in the resected liver. Adjuvant chemotherapy was able to be administered to all patients.

Comparing patients with and without conversion surgery

The clinical characteristics are compared between the patients with and without conversion surgery in Table 3. There were no statistically significant differences in the age, sex, ECOG PS, tumor location, or unresectability status (URLA vs. URM) between patients with and without surgery. The proportion of patients undergoing new regimens including FOLFIRINOX and Gnp was significantly higher among patients who underwent surgery than those who did not undergo surgery (77.8% vs. 37.3%, $p = 0.001$). The proportion of responders to non-surgical therapy was significantly higher among patients who underwent surgery than those who did not undergo surgery (100% vs. 23.8%, $p < 0.001$). Both the serum value of CA19-9 before treatment and the minimum value of CA19-9 during first-line therapy were significantly lower in patients who underwent surgery than those who did not undergo surgery (CA19-9 (1): 245.1 U/mL vs. 1391.5 U/mL, $p = 0.018$; CA19-9 (2): 23.8 U/mL vs. 343.7 U/mL, $p < 0.001$). Similarly, both the

Table 2 Outcome of patients who underwent conversion surgery (corresponding to Table 1, upper half: URLA, lower half: URM)

Case	Op	OT (min)	BL (ml)	Major complications	Hosp (days)	*R*	Tx effect (Evans)	Adj Tx	Prognosis (R/NR, months[a])	Rec site
1	DP	358	1020	POPF	56	1	2a	S1 + RT → S1	Alive (R, 49/40)	Loc
2	PD + HA + PV	621	2450	–	28	0	2b	GEM	Alive (NR, 47/37)	–
3	DP-CAR + PV	453	810	POPF	53	0	2a	S1	Dead (R, 15/11)	Loc
4	DP-CAR + PV	422	1250	POPF	116	0	2b	GEM	Alive (NR, 30/19)	–
5	PD + HA + PV	627	750	–	13	0	2a	S1	Alive (NR, 23/16)	–
6	DP	334	410	–	18	0	2a	Gnp	Alive (NR, 21/15)	–
7	PD + HA	378	590	–	21	0	3	Gnp	Alive (NR, 14/10)	–
8	DP-CAR + PV	555	1600	POPF	81	1	2b	S1	Alive (R, 18/5)	Loc, Lung
9	DP	306	520	POPF	64	0	2a	S1	Alive (R, 62/42)	Loc
10	DP + Hep	398	930	–	19	0	2a	S1	Alive (NR, 46/38)	–
11	DP-CAR	284	300	POPF	89	0	2b	S1	Alive (NR, 38/31)	–
12	DP-CAR	450	1190	POPF	81	0	1	Gnp	Alive (R, 36/29)	Lnd
13	PD + Hep	521	650	–	21	0	4	S1	Alive (R, 29/23)	Liv
14	DP	258	165	POPF	28	0	4	S1	Alive (NR, 25/19)	–
15	DP-CAR + PV	572	1400	–	18	0	2a	S1	Alive (R, 15/7)	Per
16	PD	551	1250	–	26	0	3	S1	Alive (NR, 17/7)	–
17	DP	456	620	–	30	0	2b	S1	Alive (NR, 17/1)	–
18	PD	450	600	–	47	0	2a	FFX	Alive (NR, 13/7)	–

Op operative procedure, *OT* operative time, *BL* blood loss, Hosp: hospitalization, *R* residual tumor status, *Tx effect* treatment effect, *Adj Tx* adjuvant therapy, *R/NR* recurrence/non-recurrence, *Rec site* recurrence site, *DP* distal pancreatectomy, *POPF* postoperative pancreatic fistula, *Loc* local, *RT* radiation therapy, *HA* hepatic artery, *PV* portal vein, *DGE* delayed gastric emptying, *GEM* gemcitabine, *Hep* hepatectomy, *DP-CAR* distal pancreatectomy with en bloc celiac axis resection, *Lnd* lymph node, *Liv* liver, *Per* peritoneum, *Gnp* gemcitabine + nab-paclitaxel

[a]Months after the diagnosis/months after conversion surgery

Table 3 A comparison of the clinical characteristics between CS and non-CS patients

	CS (n=18)	Non-CS (n=416)	p
Age, years	66 (45 to 73)	65 (28 to 88)	0.680
Sex (male)	7 (38.9%)	243 (58.4%)	0.142
PS (0)	18 (100%)	355 (85.3%)	0.090
Location (Ph)	6 (33.3%)	154 (37.0%)	0.809
IR status (URM)	10 (55.6%)	314 (75.5%)	0.091
New regimens	14 (77.8%)	155 (37.3%)	0.001
Responders	18 (100%)	99 (23.8%)	<0.001
Albumin, g/dl	4.1 (3.2 to 5.0)	4.1 (1.6 to 5.2)	0.564
CA19-9 (1), U/ml	245.1 (0.1 to 4780.0)	1391.5(0.1 to 999999.9)	0.018
CA19-9 (2), U/ml	23.8 (0.1 to 86.5)	343.7 (0.1 to 999999.9)	<0.001
CA19-9 LR	91.2% (0 to 99.3%)	43.3% (-1243.6 to 99.9%)	<0.001
Tumor size (1), mm	25.2 (12.9 to 36.4)	33.9 (13.0 to 103.1)	<0.001
Tumor size (2), mm	11.6 (5.8 to 18.7)	29.3 (0 to 96.8)	<0.001
Tumor size-LR	52.4% (19.4 to 71.6%)	8.1% (− 95.2 to 100%)	<0.001

CS conversion surgery, *PS* performance status, *Ph* pancreatic head, *IR* irresectability, *URM* unresectable metastatic, *CA19-9 (1)* value of CA19-9 before treatment, *CA19-9 (2)* minimum value of CA19-9, *LR* lowering rate, *tumor size (1)* tumor size before treatment, *tumor size (2)* minimum tumor size

tumor size before treatment and the minimum tumor size during first-line therapy were significantly lower in patients who underwent surgery than those who did not undergo surgery (tumor size (1): 25.2 mm vs. 33.9 mm, $p<0.001$; tumor size (2): 11.6 mm vs. 29.3 mm, $p<0.001$). Furthermore, the LRs of CA19-9 and the tumor size were significantly higher in patients who underwent surgery than those who did not undergo surgery (CA19-9-LR: 91.2% vs. 43.3%, $p<0.001$; tumor size-LR: 52.4% vs. 8.1%, $p<0.001$). The survival rate was significantly better in patients who underwent conversion surgery than in those who did not (MST: not reached vs. 337 days; 3-year survival rate: 78.1% vs. 5.8%; hazard ratio [HR]: 0.07, 95% confidence interval [CI] 0.02–0.27, $p<0.001$) (Fig. 1A).

In the multivariate analysis, the performance of conversion surgery (HR 0.15, 95% CI 0.04–0.62, $p=0.009$), serum value of albumin (HR 0.66, 95% CI 0.50–0.88, $p=0.004$), log10 (CA19-9(1)) (HR 1.20, 95% CI 1.01–1.23, $p=0.035$), log10(tumor size(1)) (HR 4.95, 95% CI 2.24–10.93, $p<0.001$), CA19-9-LR (HR 0.76, 95% CI 0.71–0.81, $p<0.001$), and tumor size-LR (HR 0.26, 95% CI 0.15–0.45, $p<0.001$) were shown to be significantly correlated with the OS (Table 4). The median observation period for patients with surgery was 899.5 days.

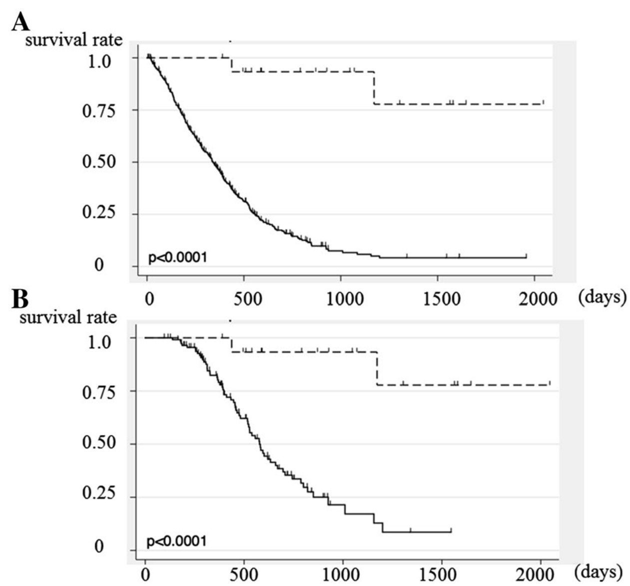

Fig. 1 **a** The survival rate was significantly better in patients who underwent conversion surgery than in those who did not. **b** Even when the cohort was limited to responder patients (n=117), the survival rate was significantly better in patients who underwent conversion surgery than in those who did not. Solid line: patients who underwent surgery. Dotted line: patients who did not undergo surgery

Responder patients

Among 434 patients with URPca, the treatment effect of first-line therapy according to the RECIST classification was PR in 117 and CR (complete response) in 0 patients. Thus, the number of responder patients was 117 (27.0%). Even when the cohort was limited to responder patients (n=117), the survival rate was significantly better in patients who underwent conversion surgery than in those who did not (MST: not reached vs. 562 days; 3-year survival rate: 78.1% vs. 16.6%; HR 0.09, 95% CI 0.02–0.37, $p<0.001$) (Fig. 1b). In the multivariate analysis, the performance of conversion surgery (HR 0.14, 95% CI 0.03–0.60, $p=0.008$), log10(tumor size(1)) (HR 10.58, 95% CI 1.56–71.90,

Table 4 Predictive factors for the overall survival of patients with URPca

	Univariate analysis			Multivariate analysis[a]		
	HR	95% CI	*p*	HR	95% CI	*p*
CS (Yes)	0.07	0.02–0.27	< 0.001	0.15	0.04–0.62	0.009
New regimen (Yes)	0.55	0.44–0.69	< 0.001	0.83	0.62–1.12	0.223
PS (1 or 2)	1.73	1.29–2.33	< 0.001	1.26	0.86–1.87	0.237
Age (per year)	1.01	1.00–1.02	0.018	1.01	0.995–1.02	0.230
Sex (male)	1.19	0.96–1.48	0.116	0.93	0.73–1.20	0.591
Location (Ph)	0.98	0.79–1.23	0.877	0.96	0.73–1.28	0.789
UR status (URM)	1.70	1.32–2.20	< 0.001	1.27	0.95–1.69	0.111
Alb (per mg/dl)	0.58	0.47–0.73	< 0.001	0.66	0.50–0.88	0.004
Log10 (CA19-9 [1])	1.24	1.14–1.36	< 0.001	1.20	1.01–1.23	0.035
Log10 (tumor size [1])	5.85	3.11–11.02	< 0.001	4.95	2.24–10.93	< 0.001
CA19-9-LR	0.73	0.69–0.77	< 0.001	0.76	0.71–0.81	< 0.001
Tumor size-LR	0.16	0.11–0.25	< 0.001	0.26	0.15–0.45	< 0.001

URPca unresectable pancreatic cancer, *HR* hazard ratio, *CI* confidence interval, *CS* conversion surgery, *PS* performance status, *Ph* pancreatic head, *UR* unresectability, *URM* unresectable metastatic, *CA19-9 (1)* value of CA19-9 before treatment, *tumor size (1)* tumor size before treatment, *LR* lowering rate

p = 0.016), and CA19-9-LR (HR 0.28, 95% CI 0.11–0.74, *p* = 0.010) were shown to be significantly correlated with the OS (Table 5).

Discussion

Regarding the terminology used in this document, we distinguish between 'conversion surgery' and 'adjuvant surgery'. We believe that 'adjuvant surgery' should be used for planned surgery that is sequentially performed after preoperative neoadjuvant therapy for patients who were always known to be suitable for surgery. In contrast, 'conversion surgery' should be used for unplanned surgery that is performed as a result of 'strategy conversion' due to an unexpected strong anticancer effect with non-surgical therapy. In this respect, we performed 'conversion surgery' (not 'adjuvant surgery') for 18 patients in our series, as we had not considered them to be candidates for future surgery at their treatment initiation.

This study is valuable in the terms of showing the 'real resection rate' for patients with URPca. Most previous studies calculated the resection rate using a limited population receiving neoadjuvant therapy as the denominator. However, we included all (consecutive) patients with URPca who received palliative therapy and calculated the rate using the

Table 5 Predictive factors for the overall survival of 'responder patients' with URPca

	Univariate analysis			Multivariate analysis[a]		
	HR	95% CI	*p*	HR	95% CI	*p*
CS (Yes)	0.09	0.02–0.37	0.001	0.14	0.03–0.60	0.008
New regimen (Yes)	0.90	0.53–1.54	0.708	0.93	0.49–1.76	0.823
PS = 1 or 2	1.40	0.64–3.08	0.399	1.16	0.47–2.88	0.742
Age (per year)	0.99	0.97–1.02	0.652	1.01	0.98–1.04	0.666
Sex (male)	1.20	0.73–1.95	0.474	1.09	0.58–2.06	0.795
Location (Ph)	1.05	0.63–1.78	0.844	1.35	0.65–2.78	0.420
UR status (URM)	1.04	0.63–1.72	0.874	1.19	0.66–2.13	0.565
Alb (per mg/dl)	0.85	0.51–1.41	0.523	1.04	0.54–2.00	0.905
Log10 (CA19-9 [1])	1.26	1.02–1.57	0.034	1.20	0.95–1.51	0.132
Log10 (tumor size [1])	14.64	3.33–64.35	< 0.001	10.58	1.56–71.90	0.016
CA19-9-LR	0.38	0.17–0.88	0.023	0.28	0.11–0.74	0.010
Tumor size-LR	1.55	0.37–6.48	0.550	2.14	0.44–10.32	0.345

URPca unresectable pancreatic cancer, *HR* hazard ratio, *CI* confidence interval, *CS* conversion surgery, *PS* performance status, *Ph* pancreatic head, *UR* unresectability, *URM* unresectable metastatic, *CA19-9 (1)* value of CA19-9 before treatment, *tumor size (1)* tumor size before treatment, *LR* lowering rate total population as the denominator. As a result, the resection rate in our study was only 4.1% (URLA: 7.3%, URM: 3.1%). However, this value was still much lower than that in previous studies, even considering the difference in the denominator. One possible reason for this discrepancy may be a difference in policy, with surgery indicated for patients with URPca. Most previous studies have highlighted the effectiveness of aggressive adjuvant surgery, while basically did not considered patients with URPca to be candidates for surgery and instead performed conversion surgery only for a very limited pool of patients, namely those who were 'super-responders' to palliative treatment. The high resection rate reported in most studies was, therefore, the rate of achieving adjuvant surgery, while the resection rate reported in the present study was instead the 'real conversion surgery rate' for the total cohort of patients with URPca.

Hackert et al. [5] reported that, among 575 patients with locally advanced pancreatic cancer who received neoadjuvant therapy, pancreatic resection was able to be performed in 292 (50.8%) patients, which was a much higher resection rate than in our series. However, in their data, the MST after adjuvant surgery was reported to be only 15.3 months. Even when taking the period between the initial diagnosis and adjuvant surgery (median 154 days) into consideration, the MST after the diagnosis was only roughly 20 months, which is unsatisfactory, considering the fact that the MST of patients with URLA disease treated with non-surgical therapy was reported to be 15–17 months in recent phase 2 studies [19–21]. We, therefore, believe that complex and invasive pancreatic resection for such advanced disease should be justified only for a very limited group of patients who have the potential to achieve a reasonable survival duration after surgery. Another possible reason for the lower resection rate in our study is that we used new anticancer regimens including Gnp ($n = 124$) and FOLFIRINOX ($n = 45$) for only 38.9% (164/434) of patients, as these regimens were unavailable during the first half of our study. When the cohort was limited to patients treated with new anticancer regimens, conversion surgery was able to be performed for 14 (8.3%) patients. The number of conversion surgeries has been increasing annually (2012: $n = 1$, 2013: n = 1, 2014: $n = 3$, 2015: $n = 5$, 2016: $n = 4$, and 2017: $n = 4$), possibly due to the increasing usage of these regimens.

Several studies have demonstrated a survival benefit of adjuvant or conversion surgery for patients with URPca [5, 11, 22–24]. Satoi et al. [23] compared 58 patients who underwent adjuvant surgery and 101 patients who did not undergo surgery and revealed that the survival in the adjuvant surgery group was significantly better than that in the non-surgery group according to their multicenter survey. We also showed that the survival was significantly better in patients who underwent conversion surgery than in those who did not.

However, caution must be practiced when interpreting this survival difference due to bias potentially existing between patients with and without surgery. At the pre-treatment stage, patients who eventually underwent surgery were in a significantly better oncological condition than those who did not ultimately undergo surgery. In addition, not surprisingly, patients who eventually underwent surgery may have had a higher sensitivity to non-surgical treatment than those who did not undergo surgery. In our study, the LRs of CA19-9 and tumor size were significantly better in patients who eventually underwent surgery than in those who did not undergo surgery. Because conversion surgery is indicated only for patients who respond to non-surgical therapy, the survival superiority of patients who eventually underwent surgery over those who did not undergo surgery may have resulted from a difference in chemo-sensitivity. Therefore, the next research question was 'Does performing conversion surgery really have a positive prognostic impact even when the cohort is limited to responders to non-surgical therapy?'

To investigate this issue, we identified 'responder patients'—those who responded to first-line non-surgical therapy ($n = 117$; 39.2%). Even when limiting the cohort to responders, the survival rate was significantly better in patients who underwent conversion surgery than in those who did not. Furthermore, conversion surgery was significantly correlated with the survival in a multivariate analysis, even among responder patients. Of course, in our study, further bias may have existed between patients with and without conversion surgery, even when limiting the cohort to responders. Patients who underwent conversion surgery had to meet the following conditions: R0 resection feasible for the local lesion, at least 6 months of disease control, and no metastatic lesions detected on imaging studies. In other words, conversion surgery was performed only for 'super-responder patients', as surgery could not be performed for 'usual-responder patients'.

Regarding the indications of conversion surgery for URLA disease, we have been considering the 'possibility of performing R0 resection' as a strategy to achieve tumor reduction in cases of either resectable or borderline resectable disease. We do not treat patients in whom the tumor makes contact with a major artery > 180° after chemotherapy as candidates for surgery, even when the local tumor is controlled without growth for over 6 months. Recently, Lee et al. [25] reported an excellent outcome, showing that 15 of 64 (23.4%) patients with URLA Pca underwent conversion surgery with an OS exceeding 40 months, although they did not describe the indications for surgery clearly. We may need to expand our surgical indication, particularly concerning patients with locally advanced disease, if favorable outcomes continue to be reported from more aggressive centers hereafter.

There are several limitations associated with the present study, including its retrospective nature, the limited follow-up, and the relatively small sample size, especially for patients who underwent conversion surgery.

In conclusion, satisfactory outcomes were able to be achieved for highly select patients with URPca in exchange for a reduced resection rate (4.1%).

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

References

1. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al, JASPAC 01 Study Group. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2016;388:248–57.
2. Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008;206:833–46.
3. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. Groupe tumeurs digestives of unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817–25.
4. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691–703.
5. 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;264:457–63.
6. Marthey L, Sa-Cunha A, Blanc JF, Gauthier M, Cueff A, Francois E, et al. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. Ann Surg Oncol. 2015;22:295–301.
7. Huguet F, Hajj C, Winston CB, Shi W, Zhang Z, Wu AJ, et al. Chemotherapy and intensity-modulated radiation therapy for locally advanced pancreatic cancer achieves a high rate of R0 resection. Acta Oncol. 2017;56:384–90.
8. 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;22:1212–20.
9. Moorcraft SY, Khan K, Peckitt C, Watkins D, Rao S, Cunningham D, et al. FOLFIRINOX for locally advanced or metastatic pancreatic ductal adenocarcinoma: the Royal Marsden experience. Clin Colorectal Cancer. 2014;13:232–8.
10. Peddi PF, Lubner S, McWilliams R, Tan BR, Picus J, Sorscher SM, et al. Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma. JOP. 2012;13:497–501.
11. Blazer M, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P, et al. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. Ann Surg Oncol. 2015;22:1153–9.
12. Nanda RH, El-Rayes B, Maithel SK, Landry J. Neoadjuvant modified FOLFIRINOX and chemoradiation therapy for locally advanced pancreatic cancer improves resectability. J Surg Oncol. 2015;111:1028–34.
13. Boone BA, Steve J, Krasinskas AM, Zureikat AH, Lembersky BC, Gibson MK, et al. Outcomes with FOLFIRINOX for borderline resectable and locally unresectable pancreatic cancer. J Surg Oncol. 2013;108:236–41.
14. Japan Pancreas Society. General rules for the study of pancreatic cancer. 7th ed. Tokyo: Kanehara shuppan; 2016.
15. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–16.
16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a surgery. Ann Surg. 2004;240:205–13.
17. Bassi C, Marchegiani G, Derveins C, Sarr M, Abu Hial M, Adham M, et al. The 2016 updated of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2017;161:584–91.
18. Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg. 1992;127:1335–9.
19. 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;19:152–8.
20. Sudo K, Yamaguchi T, Ishihara T, Nakamura K, Hara T, Denda T, et al. Phase II study of oral S-1 and concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2011;80:119–25.
21. Ishii H, Furuse J, Boku N, Okusaka T, Ikeda M, Ohkawa S, et al. Phase II study of gemcitabine chemotherapy alone for locally advanced pancreatic carcinoma: JCOG0506. Jpn J Clin Oncol. 2010;40:573–9.
22. Sho M, Akahori T, Tanaka T, Kinoshita S, Nagai M, Tamamoto T, et al. Importance of resectability status in neoadjuvant treatment for pancreatic cancer. J Hepatobiliary Pancreat Sci. 2015;22:563–70.
23. 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 a long-term favorable response to non-surgical anti-cancer treatments: results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci. 2013;20:590–600.
24. Opendro SS, Satoi S, Yanagimoto H, Toyokawa H, Hirooka S, Yamaki S, et al. Role of adjuvant surgery in initially unresectable pancreatic cancer after long-term chemotherapy or chemoradiation therapy: survival benefit? J Hepatobiliary Pancreat Sci. 2014;21:695–702.
25. Lee J, Lee JC, Gromski MA, Kim HW, Kim J, Hwang JH. Clinical outcomes of FOLFIRINOX in locally advanced pancreatic cancer: a single center experience. Medicine. 2018;97:e13592.