Review

DOI: 10.5582/bst.2022.01250

Trends in the surgical treatment for pancreatic cancer in the last 30 years

Ryota Matsuki[1], Naohiro Okano[2], Nobuhiro Hasui[1], Shohei Kawaguchi[1], Hirokazu Momose[1], Masaharu Kogure[1], Yutaka Suzuki[1], Fumio Nagashima[2], Yoshihiro Sakamoto[1,*]

[1] Department of Hepato-Biliary-Pancreatic Surgery, Kyorin University Hospital, Tokyo, Japan;
[2] Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan.

SUMMARY Pancreatic cancer has the poorest prognosis among digestive cancers. During the 1990s, the 5-year survival rate of surgical patients with pancreatic cancer was 14% in Japan. However, survival rates have increased to 40% in the 2020s due to the refinement of surgical procedures and the introduction of perioperative chemotherapy. Several pivotal randomized controlled trials have played an indispensable role to establish each standard treatment strategy. Resectability of pancreatic cancer can be classified into resectable, borderline resectable, and unresectable based on the anatomic configuration, and multidisciplinary treatment strategies for each classification have been revised rapidly. Investigation of superior perioperative adjuvant treatments for resectable and borderline resectable pancreatic cancer and the establishment of optimal conversion surgery for unresectable pancreatic cancer are the progressive subjects.

Keywords pancreatic cancer, multidisciplinary treatment, resectability, perioperative adjuvant therapy, conversion surgery

1. Introduction

Pancreatic cancer (PC) is known to have the poorest prognosis among all digestive cancers. Although surgical resection is the only feasible treatment to cure this disease, only 15-20% of PC cases are resectable at the time of the first diagnosis, while 30-40% are locally advanced cases and 50-60% are distant metastatic cases (*1*). The latter two cohorts are initially unresectable.

In the 1990s, a Japanese nationwide survey showed that the overall 5-year survival rate in patients undergoing radical resection for PC was 14% (*2*). Nowadays, the 5-year survival rate of resectable PC has increased to 40% (*3*) owing to the gradual refinement of surgical procedures and the subsequent introduction of perioperative chemotherapy. In this chapter, we review the pivotal surgical approaches that have contributed to the advancement of multidisciplinary treatment for PC.

2. Limitations of extended resection for PC

During the 1990s, there was no effective chemotherapy for PC in Japan. Hence, radical pancreatectomy combined with extended lymphadenectomy, including the paraaortic lymph nodes and nerve plexus dissection around major peripancreatic arteries, were performed for PC to eradicate cancer cells completely and to improve patient survival (*4-8*). This concept was originally advocated by Fortner who had originally started radical resection for PC in the 1970s (*9,10*). However, the short- and long-term survival rates of patients with PC were far from satisfactory, fomenting controversy regarding the advantages and disadvantages of radical pancreatectomy combined with extensive nodal and/or nerve dissection and controversy because aggressive dissection was associated with increased morbidities.

To resolve the above clinical question, randomized clinical trials (RCTs) were then performed to reveal the prognostic superiority of extended radical pancreatectomy against standard pancreatectomy for PC. A total of five RCTs on the extent of dissection during pancreatectomy were conducted between 1991 and 2009 (Table 1) (*11-15*). Results showed no significant difference in the overall survival (OS) between the extended and standard lymphadenectomy groups in the five RCTs, *i.e.*, none of the RCTs revealed any prognostic advantage of extended lymphadenectomy against standard lymphadenectomy during pancreatectomy for PC. With respect to surgical complications, no significant differences were found in the incidence of surgical morbidity and mortality between the two groups, except for the series performed in Johns Hopkins Hospital, in

Table 1. The results of 5 RCTs comparing standard and extended pancreatectomy

Author	Year	Procedure of extended resection	Number Extended *vs.* Standard	Median OS (months)	Morbidity and Mortality
Pedrazzoli *et al*. (*11*)	1991-1994	Lymphadenectomy	41 *vs*. 40	500 days *vs*. 355 days NS	Morbidity: NS Mortality: 4.8% *vs*. 5%, NS
Yeo *et al*. (*12*)	1996-2001	Lymphadenectomy Distal gastrectomy	148 *vs*. 146	20 *vs*. 21 NS	Morbidity: 49% *vs*. 29%, $p = 0.01$ Mortality: 2% *vs*. 4%, $p = 0.30$
Farnell *et al*. (*13*)	1997-2003	Lymphadenectomy	39 *vs*. 40	19 *vs*. 26, $p = 0.32$	Morbidity: NS Mortality: 3% *vs*. 0%, NS
Nimura *et al*. (*14*)	2000-2003	Lymphadenectomy	50 *vs*. 51	13.8 *vs*. 19.9 $p = 0.119$	Morbidity: 22% *vs*. 20%, NS Mortality: 2% *vs*. 0%, NS
Jang *et al*. (*15*)	2006-2009	Lymphadenectomy Nerve plexus, Ganglion	86 *vs*. 83	18.0 *vs*. 19.0 $p = 0.401$	Morbidity: 43% *vs*. 32.5%, $p = 0.16$ Mortality: 2.3% *vs*. 0%, NS

NS: not significant.

which the morbidity rate was higher in the extended compared to the standard group (49% *vs*. 29%, $p = 0.01$) (*11*). These results suggested no oncological advantage for extended lymphadenectomy in pancreatectomy for PC, and the researchers' concern gradually shifted from radical surgical resection to employing a multidisciplinary treatment for PC.

3. Development of multidisciplinary treatment for PC

3.1.Adjuvant chemotherapy for PC following resection

With regard to adjuvant chemotherapy for PC following resection, several RCTs comparing adjuvant 5-fluorouracil (5-FU) based chemotherapy with surgery alone were conducted in the 1990s. In a trial of adjuvant 5-FU plus mitomycin treatment *vs*. surgery alone, the 5-year survival rate was 11.5% in the adjuvant 5-FU plus mitomycin group and 18.0% in the surgery alone group, showing no significant difference (*16*). Similarly, another trial of adjuvant 5-FU plus cisplatin *vs*. surgery alone revealed that the 5-year survival rate was 11.5% in the adjuvant 5-FU plus cisplatin group and 18.0% in the surgery alone group, also showing no significant difference (*17*).

In 1997, the prognostic superiority of gemcitabine (GEM) treatment over 5-FU for unresectable (UR) PC was reported (*18*). This result was followed by clinical trials administering GEM as an adjuvant setting for resectable PC (*19*). In 2007, a trial of adjuvant GEM *vs*. surgery alone (CONKO-001) conducted in Germany showed a significant increase in the recurrence-free survival in the adjuvant GEM group (median, 13.4 months *vs*. 6.7 months, $p < 0.001$) and a significant increase in OS in the adjuvant GEM group during follow-up (22.8 months *vs*. 20.2 months, $p = 0.01$) (*20*). In a Japanese trial of GEM *vs*. surgery alone (JSAP-02 trial), no significant difference was found in the OS between the two groups (median, 22.3 months *vs*. 18.4 months, $p = 0.19$), but the disease-free survival (DFS) was significantly longer in the GEM group (median, 11.4 months *vs*. 5.0 months, $p = 0.01$) (*21*). Since the announcement of these positive results, adjuvant GEM therapy has become the standard therapy for resectable PC in Japan at the beginning of the 2010s.

Meanwhile, several RCTs of adjuvant chemotherapies were conducted in comparison with adjuvant GEM therapy for resectable PC (Table 2) (*3,22-25*). In the ESPAC-4 trial, the OS in the adjuvant GEM + Capecitabine (Cape) group was significantly improved compared with the adjuvant GEM group (28.0 months *vs*. 25.5 months, $p = 0.032$) (*23*). Based on these findings, the ASCO, NCCN, and ESMO guidelines started to recommend GEM + Cape as the standard adjuvant therapy for resectable PC. In Japan, the JASPAC-01 trial revealed that the OS in adjuvant S-1 groups was significantly improved compared to adjuvant GEM group (25.5 months *vs*. 46.5 months, $p < 0.0001$) (*3*). As a result, the Japanese guidelines recommended S-1 as the standard adjuvant therapy for resectable PC (*26*).

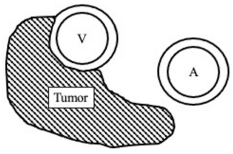
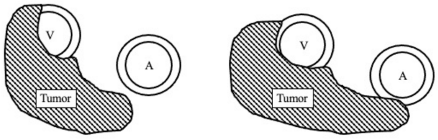
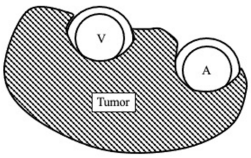
Since 2011, the modified FOLFIRINOX (mFFX) therapy has become one of the leading regimens for UR PC with distant metastasis (*27*). This regimen has also been utilized in adjuvant therapy for resectable PC. The PRODIGE24-ACCORD24 and CCTG PA6 trials revealed that the DFS (21.6 months *vs*. 12.8 months, $p < 0.0001$) and OS (54.4 months *vs*. 35.0 months, $p = 0.003$) were significantly prolonged in the mFFX group compared to the GEM group. As a result, the NCCN and ESMO guidelines recommended adjuvant mFFX for resectable PC (*24*). GEM + nab-paclitaxel therapy (GnP) has been another leading regimen for unresectable PC since 2013 (*28*). A trial of adjuvant GEM *vs*. GnP was conducted in the United States, whose results were reported at ASCO 2019 annual meeting (*25*). In an interim analysis, the OS was significantly improved in the GnP group compared to the GEM group (40.5 months *vs*. 36.2 months, $p = 0.045$). Further studies on adjuvant therapy are expected to improve the outcomes of resectable PC in the future.

Table 2. The results of RCTs comparing with GEM in adjuvant chemotherapy

Author	Year	Regimen	Number	Primary endpoint	DFS				OS			
					Months	HR	95%CI	*p*-value	Months	HR	95%CI	*p*-value
Moore *et al*.	2007	GEM	217	DFS	11.4	0.94	0.76-1.15	0.26	26.5	-	-	0.61
CONKO-005 (*22*)		GEM+Elro	219		11.4				24.5			
Neoptolemos *et al*.	2017	GEM	366	OS	13.1	0.86	0.73-1.02	0.082	25.5	0.82	0.68-0.98	0.032
ESPAC-04 (*23*)		GEM+Cape	354		13.9				28.0			
Uesaka *et al*.	2016	GEM	193	OS	11.3	0.60	0.47-0.76	< 0.001	25.5	0.57	0.44-0.72	< 0.001
JASPAC 01 (*3*)		S-1	192		22.9				46.5			
Conroy *et al*.	2018	GEM	246	DFS	12.8	0.58	0.46-0.73	< 0.001	35.0	0.64	0.48-0.86	0.003
PRODIGE24 (*24*)		mFOLFIRINOX	247		21.6				54.4			
Tempero *et al*.	2019	GEM	434	DFS	18.8	0.88	0.73-1.06	0.182	36.2	0.82	0.68-1.00	0.045
APACT (*25*)	in ASCO	GnP	432		19.4				40.5			

Cape: capecitabine, CI: confidence interval, DFS: disease-free survival, Erlo: erlotinib, GEM: gemcitabine, GnP: gemcitabine plus nab-paclitaxel, HR: hazard ratio, mFOLFIRINOX: modified FOLFIRINOX, OS: overall survival, RCT: randomized control trial.

Table 3. International consensus of classification of resectability in pancreatic cancer based on anatomical definition using CT imaging

Resectable (R)	SMV/PV: no tumor contact or unilateral narrowing; SMA, CA, CHA: no tumor contact.	
Borderline resectable (BR)		
BR-PV SMV/PV involvement alone	SMV/PV ▪ Tumor contact 180°or greater; ▪ Bilateral narrowing/occlusion, not exceeding the inferior border of the duodenum; SMA, CA, CHA: no tumor contact/invasion;	
BR-A Artery involvement	SMA, CA: tumor contact of less than 180°without showing deformity/stenosis; CHA: tumor contact without showing tumor contact of the PHA and/or CA.	
Unresectable (UR)		
Locally advanced (LA)	SMV/PV: bilateral narrowing/occlusion, exceeding the inferior border of the duodenum; SMA, CA: tumor contact / invasion of 180°or more; CHA: tumor contact/invasion showing tumor contact/ invasion of the PHA and/or CA; Ao: tumor contact or invasion .	

3.2.Establishing the definition of resectability for PC

At the beginning of the 2000's, an attempt was made to classify PC into categories according to their resectability. Resectability of PC was first classified in the NCCN guidelines in 2004, and further objective classification based on the anatomical extension on computed tomography (CT) images was proposed by M. D. Anderson Cancer Center (MDACC) in 2006 (*29*). Briefly, all PCs were classified into resectable (R), borderline resectable (BR), and unresectable (UR) based on the local extension and presence or absence of distant metastasis (Table 3). In the 20th meeting of the International Association of Pancreatology in Japan (2016), the International consensus on the classification of BR PC was defined based on anatomical configurations on CT imaging (*30*). Nowadays, the treatment strategy for PC is determined by the resectability status at the time of diagnosis, and a multidisciplinary treatment strategy is a key for successful treatment for PC.

3.3. Neoadjuvant therapy for BR or R PC

In cases of R/BR PC, chemo (radiation) therapy can be performed as neoadjuvant therapy on the assumption

that surgery is to be performed. Possible advantages of neoadjuvant therapy for R/BR PC include the following: 1) it is a more aggressive treatment option compared to adjuvant therapy, 2) has the potential for improved resectability and R0 rate due to tumor shrinkage, 3) can control potential nodal or distant metastases, and 4) can select the ineligibility for radical resection. Many researchers have attempted to clarify the efficacy of neoadjuvant therapy, and several RCTs for R/BR PC have been conducted (Table 4) (*31-34*). Motoi *et al*. in Japan reported that preoperative chemotherapy by GEM plus S-1 for R/BR PC significantly prolonged OS compared to upfront surgery (median, 36.7 months *vs*. 26.7 months, $p = 0.015$) (*34*). However, the remaining three RCTs did not demonstrate the survival superiority of neoadjuvant therapy compared to upfront surgery in the treatment of R/BR PC (*31-33*). Therefore, the true impact of neoadjuvant therapy for R PC still remains controversial. Table 5 shows the ongoing RCTs of neoadjuvant therapy for R PC (*35-39*), and the results of these trials may resolve this controversy in the near future.

Neoadjuvant chemo(radiation) therapy for BR PC was introduced before surgery relatively earlier than for R PC, because it is sometimes difficult to obtain negative margins in upfront surgery for BR PC. In 2008, Katz *et al*. in MDACC classified BR PC into three groups (Type A, B, and C) based on local anatomic factors, tumor factors, and patient factors, and investigated the effect of preoperative chemoradiotherapy on these factors. The authors found that patients who were re-classified as resectable after preoperative chemoradiotherapy had improved survival rates in all three groups (*40*). According to the multi-institutional survey data presented by the Japanese society of pancreatic surgery, the OS of 57 patients among 539 patients with resected BR PC who underwent preoperative treatment was significantly improved compared to the remaining 482 patients who did not (median, 12.1 months *vs*. 23.8 months, $p = 0.023$) (*41*). Nagakawa *et al*. also reported significantly better survival rates in the preoperative treatment group ($n = 297$) than in the non-treatment group ($n = 297$) in a multicenter retrospective study using propensity score matching (median OS, 25.7 months *vs*. 19.0 months, $p = 0.015$) (*42*).

Table 4. RCTs of neoadjuvant therapy for resectable / borderline resectable pancreatic cancer

Author	Year	Country	Resectability	Regimen	Number	Number of resection (%)	R0 resection (%)	Median OS (months)
Golcher *et al*. (*31*)	2015	Germany	R	GEM/Cisplatin+RT Upfront surgery	33 33	19 (58) 23 (70)	52 *vs*. 48 ($p = 0.81$)	17.4 *vs*. 14.4 ($p = 0.96$)
Casadei *et al*. (*32*)	2015	Italy	R	GEM+RT Upfront surgery	18 20	11 (61) 15 (75)	39 *vs*. 25 ($p = 0.49$)	22.4 *vs*. 19.5 ($p = 0.97$)
Versteijine *et al*. (*33*)	2020	Netherlands	R/BR	GEM+RT Upfront surgery	119 127	72 (61) 92 (72)	71 *vs*. 40 ($p < 0.001$)	16.0 *vs*. 14.3 ($p = 0.096$)
Motoi *et al*. (*34*)	2019	Japan	R/BR	GEM+S-1 Upfront surgery	182 180	140 (77) 130 (72)	-	36.7 *vs*. 26.7 ($p = 0.015$)

BR: borderline resectable, R: resectable, RT: radiation therapy.

Table 5. Ongoing RCTs of neoadjutant therapy for resectable pancreatic cancer

Study	Design	Country	Resectability	Regimen	Number	Primary endpoint
NEONAX (*35*)	Phase II	Germany	R	Perioperative GnP (pre 2, post 4) Adjuvant GnP (post 6)	166	DFS at 18 months after randomization
nlTRO (*36*)	Phase II	Italy	R	Nal-IRI + 5-FU/LV + oxaliplatin (pre 3, post 3)	72	R0 resection rate
NorPACT-1 (*37*)	Phase III	Normay	R	Surgery first Preoperative FOLFIRINOX (4)	90	Overall mortality at 1year
PANACHE01-PRODIGE48 (*38*)	Phase II	France	R	FOLFINOX (pre 4, post 8) FOLFOX (pre 4, post 8) Surgery first +Adjuvant (12)	160	OS at 12 months Full therapeutic sequence
Alliance A021806 (*39*)	Phase III	USA/Canada	R	Perioperative FOLFIRINOX (pre 4, post 2) Adjuvant FOLFIRINOX (6)	352	OS

DFS: disease-free survival, GnP: gemcitabine plus nab-paclitaxel, Nal-IRI: nanoliposomal- irinotecan, LV: levofolinate, OS: overall survival, R: resectable, RCT: randomized control trial, 5-FU: 5-fluorouracil.

Table 6. Ongoing trial comparing chemotherapy and chemoradiotherapy for borderline resectable pancreatic cancer

Study	Design	Country	Regimen	Number	Primary endpoint
ALLIANCE NCT02839343	Phase II	USA	FOLFIRINOX FOLFIRINOX + SBRT	112	1.5-yaer OS
PANDAS-PRODIGE44 NCT02676349	Phase II	France	mFOLFIRINOX + Cape-base RT mFOLFIRINOX	92	R0 resection rate
GABANANCE trial	Phase II/III	Japan	GnP S-1 + RT	110	Phase II: R0 resection rate Phase III: OS

Cape: capecitabine, GEM: gemcitabine, GnP: gemcitabine plus nab-paclitaxel, mFOLFIRINOX: modified FOLFIRINOX, OS: overall survival, RT: radiation therapy, 5-FU: 5-fluorouracil.

Recent leading regimens, such as FFX and GnP, have been introduced in neoadjuvant therapy for BR PC. Miyasaka *et al*. reported that the group of neoadjuvant chemotherapy by GnP [median number of chemotherapy courses administered: 3 (1-10)] in patients with BR PC achieved a higher R0 resection rate (100% *vs*. 77%, $p = 0.01$) and better survival rate (2-year survival, 73% *vs*. 25%, $p = 0.03$) compared to the upfront surgery group (*43*). Furthermore, a meta-analysis performed by Janssen *et al*. also reported that preoperative FFX therapy in BR PC was associated with a 67.8% resection rate and 83.9% R0 resection rate, respectively, and the median survival time and progression-free survival time were 22.2 months and 18 months, respectively (*44*).

Jang *et al*. reported the results of a trial comparing neoadjuvant chemoradiotherapy (NACRT) (GEM 400 mg/m2/week + 54 Gy/6 weeks) with upfront surgery for BR PC. Results showed that the NACRT group had a higher R0 resection rate than the upfront surgery group (82% *vs*. 33% $p = 0.01$). NACRT group had a higher R0 resection rate (82.4% *vs*. 33.3%, $p = 0.01$) and a significantly better prognosis (median survival time, 21 months *vs*. 12 months, $p = 0.028$) than the upfront surgery group (*45*). Recently, the results of an RCT (PREPANIC trial) study on R/BR PC in the Netherlands showed remarkable results. The NACRT group (GEM + radiation) for BR PC showed a significantly higher R0 resection rate compared with the upfront surgery group (79% *vs*. 13%, $p < 0.01$) and significantly improved OS (median, 17.6 months *vs*. 13.2 months, $p = 0.029$) and significantly improved OS (median, 17.6 months *vs*. 13.2 months $p = 0.029$) (*46*). The results of ESPAC-5F, which is four arms prospective multicenter randomized phase II trial or upfront surgery compared with neoadjuvant therapy (GEM + Cape or FFX or chemoradiotherapy) in patients with BR-PC were reported at ASO in 2020. In this report, these neoadjuvant therapies had a significant survival benefit compared with upfront surgery (one year survival rate: 77 % *vs*. 40%, $p < 0.001$), however, resection rate and R0 resection rate were not significant differences (resection rate: 55% *vs*. 62%, $p = 0.668$, R0 resection rate: 23% *vs*. 15%, $p = 0.721$) (*47*). Still the optimal neoadjuvant therapy for BR PC remains controversial, and the ongoing RCTs including neoadjuvant chemotherapy and NACRT will be keys to solving this clinical question (Table 6).

3.4. Conversion surgery for initially UR PC

Approximately 30-40% of PCs are unresectable at the time of initial diagnosis due to locally advanced cases, and 50-60% due to the presence of distant metastases, and both groups are classified as initially unresectable, *i.e*., unresectable for locally advanced (UR-LA) and unresectable for metastasis (UR-M).

Systemic chemotherapy with/without radiotherapy is the first-line treatment for UR PC. With the development of novel chemotherapeutic agents, tumor shrinkage and control of distant metastases can be expected in UR PC. Surgical resection of initially UR PC after remission following chemo(radio)therapy is defined as conversion surgery (CS).

4. Multidisciplinary treatment for UR-LA PC

In 2020, FFX and GnP replaced the first-line chemotherapeutic regimen for patients with UR PC. The objective response rates and median OS rates of FFX and GnP were reported to be 31.6% and 23%, and 11.1 months and 8.5 months, respectively (*27,28*). Owing to the good response rates associated with these regimens, CS in patients with good responses has been gradually advanced. A meta-analysis of 13 trials of FFX for UR-LA PC reported that 91 of 325 patients (28%) underwent CS achieving 74% of R0 resection (*48*). Table 7 shows the recent results of CS for UR-LA PC, *i.e*., 20-36% of patients with UR-LA PC underwent CS after chemotherapy or chemoradiotherapy, with a median survival of 24.9-35.5 months (*49-54*). Apparently, these results highlight that optimized patient selection is bound to facilitate favorable R0 resection rates and long-term outcomes while introducing CS after effective chemotherapy in patients with initially UR-LA PC.

5. CS for UR-M PC

Table 7. Conversion surgery for unresectable locally advanced pancreatic cancer

Author	Year	Country	Regimen	Number	Number of resection (%)	R0 resection (%)	MST (months)
Sadot *et al*. (*49*)	2015	USA	FOLFIRINOX	101	31 (31)	55	25
Marthey *et al*. (*50*)	2015	France	FOLFIRINOX	77	28 (36)	-	24.9
Bednar *et al*. (*51*)	2017	USA	Various	92	19 (21)	74	32
Lee *et al*. (*52*)	2018	Korea	FOLFIRINOX	64	15 (23)	73	> 40 (NR)
Gemenetzis *et al*. (*53*)	2019	USA	FOLFIRINOX GEM-base	415	84 (20)	89	35.5
Philip PA *et al*. (*54*)	2020	USA	GnP	107	17 (16)	44	-

GEM: gemcitabine, MST: median survival time, NR: not reached.

5.1. CS seems to be more controversial for UR-M PC than for UR-LA.

There are few reports of CS for PC with synchronous metastases, which included only selected patients and poor prognoses after surgery with an approximately 10-month median OS (*55*). A small number of patients have responded remarkably well to the novel chemotherapy approach, and metastatic tumors are no longer detectable in imaging studies. Frigerio *et al*. reported that among 535 patients with UR PC with liver metastases undergoing CS, 24 patients (4.5%) with resolution of liver metastases on imaging and decreased CA19-9 levels after chemotherapy had a favorable prognosis (median OS, 56 months) (*56*). Wright *et al*. reported that among 1147 patients of UR-M PC, 23 (2.0%) patients underwent surgical resection of the primary tumor with or without metastasectomy (liver, $n = 16$; lung, $n = 6$; peritoneum, $n = 2$) after a favorable response to systematic chemotherapy. The median surgical and diagnostic OS were 18.2 and 34.1 months, respectively (*57*). Satoi *et al*. reported CS for UR-M PC with only peritoneal dissemination or positive peritoneal washing cytology. The authors treated patients with intravenous and intraperitoneal paclitaxel with S-1 before CS. The OS in eight (24.2%) of 33 patients who underwent CS was significantly higher compared to nonsurgical patients (median, 27.8 months *vs*. 14.2 months, $p = 0.0038$) (*58*). The number of patients with UR-M PC who could expect a good prognosis after CS is significantly limited, however, CS is likely to improve patient survival. To date, previous reports on CS are retrospective and involve significant bias. In addition, these reports included patient who were resected and responded well enough to chemotherapy to be considered candidates for CS, and continued chemotherapy may provide a similar prognosis. Therefore, to prove the efficacy of CS for UR PC, it is necessary to demonstrate that CS is more effective than continued chemotherapy in patients who have responded to chemotherapy and are deemed resectable. Currently, a retrospective study is being planned, mainly in Asia, to retrospectively compare patients with UR-LA or UR-M PC who have objectively responded to chemotherapy by FFX or GnP with patients who underwent CS and continued chemotherapy.

5.2. Criteria for going to CS

The optimal criteria for converting to adjuvant surgery after systemic chemotherapy with/without local radiation therapy remain unclear. As for the timing, in a retrospective multicenter study involving 97 patients with UR-LA PC in Japan, CS was more beneficial in patients with more than eight months of preoperative therapy compared to patients with less than eight months (*59*). However, this study was conducted before the introduction of FFX and GnP. Recently, Gementzis *et al*. reported that 116 (28%) of 461 patients with UR-LA PC who received FFX, GEM-based, or both chemotherapies were deemed eligible for surgery, and 84 (20%) of them were resected. The median duration of chemotherapy in the 84 patients undergoing CS was five months (range: 4-6 months) (*53*). In the Clinical Practice Guideline for Pancreatic Cancer 2019 in Japan, CS is weakly recommended for UL-LA PC (*26*) and is not defined for UR-M PC. The reported morbidity and mortality rates after CS are comparable with those after conventional pancreatectomy, and the reported survival rate of patients undergoing CS is better than patients with only chemotherapy. However, CS for UR-LA PC is technically demanding and associated with both resection and reconstruction of the portal vein, but also dissection from the superior mesenteric arteries or hepatic arteries. Thus, CS for UR PC should be performed in highly skilled institutions.

6. Conclusion

Surgical treatment results of PC have improved along with the refinement of surgical procedures and chemo/chemoradiation therapy advancements. However, many clinical questions pertaining to the optimal treatment regimen, preoperative treatment duration, and surgical resection criteria remain unresolved. The results of the ongoing prospective studies are bound to provide answers to these questions.

Funding: None.

Conflict of Interest: Naohiro Okano has received honoraria from Taiho Pharmaceutical, Eli Lilly Japan, Eisai, Bayer Yakuhin, Chugai Pharma, Ono

Pharmaceutical. Other authors have no disclosure and conflicts of interest.

References

1. Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med. 2010; 7:e1000267.
2. Egawa S, Toma H, Ohigashi H, Okusaka T, Nakao A, Hatori T, Maguchi H, Yanagisawa A, Tanaka M. Japan Pancreatic Cancer Registry; 30th year anniversary: Japan Pancreas Society. Pancreas. 2012; 41:985-992.
3. Uesaka K, Boku N, Fukutomi A, *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; 388:248-257.
4. Ishikawa O, Ohigashi H, Imaoka S, Furukawa H, Sasaki Y, Fujita M, Kuroda C, Iwanaga T. Preoperative indications for extended pancreatectomy for locally advanced pancreas cancer involving the portal vein. Ann Surg. 1992; 215:231-236.
5. Kayahara M, Nagakawa T, Ueno K, Ohta T, Takeda T, Miyazaki I. An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. Cancer. 1993; 72:2118-2123.
6. Nagakawa T, Nagamori M, Futakami F, Tsukioka Y, Kayahara M, Ohta T, Ueno K, Miyazaki I. Results of extensive surgery for pancreatic carcinoma. Cancer. 1996; 77:640-645.
7. Henne-Bruns D, Vogel I, Lüttges J, Klöppel G, Kremer B. Ductal adenocarcinoma of the pancreas head: survival after regional versus extended lymphadenectomy. Hepatogastroenterology. 1998; 45:855-866.
8. Iacono C, Accordini S, Bortolasi L, Facci E, Zamboni G, Montresor E, Marinello PD, Serio G. Results of pancreaticoduodenectomy for pancreatic cancer: extended versus standard procedure. World J Surg. 2002; 26:1309-1314.
9. Fortner JG. Regional resection of cancer of the pancreas: a new surgical approach. Surgery. 1973; 73:307-320.
10. Fortner JG, Kim DK, Cubilla A, Turnbull A, Pahnke LD, Shils ME. Regional pancreatectomy: en bloc pancreatic, portal vein and lymph node resection. Ann Surg. 1977; 186:42-50.
11. Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, Klöppel G, Dhaene K, Michelassi F. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg. 1998; 228:508-517.
12. Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, Coleman J, Abrams RA, Hruban RH. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg. 2002; 236:355-366.
13. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, Foster N, Sargent DJ; Pancreas Cancer Working Group. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery. 2005; 138:618-28; discussion 628-30.
14. Nimura Y, Nagino M, Takao S, *et al*. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepatobiliary Pancreat Sci. 2012; 19:230-241.
15. Jang JY, Kang MJ, Heo JS, Choi SH, Choi DW, Park SJ, Han SS, Yoon DS, Yu HC, Kang KJ, Kim SG, Kim SW. A prospective randomized controlled study comparing outcomes of standard resection and extended resection, including dissection of the nerve plexus and various lymph nodes, in patients with pancreatic head cancer. Ann Surg. 2014; 259:656-664.
16. Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, Nagakawa T, Nakayama T; Study Group of Surgical Adjuvant Therapy for Carcinomas of the Pancreas and Biliary Tract. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer. 2002; 95:1685-1695.
17. Kosuge T, Kiuchi T, Mukai K, Kakizoe T; Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP). A multicenter randomized controlled trial to evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. Jpn J Clin Oncol. 2006; 36:159-165.
18. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol. 1997; 15:2403-2413.
19. Oettle H, Post S, Neuhaus P, *et al*. Adjuvant chemotherapy with gemcitabine *vs* observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007; 297:267-277.
20. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, Niedergethmann M, Zülke C, Fahlke J, Arning MB, Sinn M, Hinke A, Riess H. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013; 310:1473-1481.
21. Ueno H, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, Doi R, Monden M, Hatori T, Tanaka M, Shimada M, Kanemitsu K. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. Br J Cancer. 2009; 101:908-915.
22. Sinn M, Bahra M, Liersch T, *et al*. CONKO-005: Adjuvant Chemotherapy With Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: A Multicenter Randomized Phase III Trial. J Clin Oncol. 2017; 35:3330-3337.
23. Neoptolemos JP, Palmer DH, Ghaneh P, *et al*. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017; 389:1011-1024.

24. Conroy T, Hammel P, Hebbar M, *et al*. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med. 2018; 379:2395-2406.
25. Tempero MA, Reni M, Riess H, *et al*. APACT: Phase III, multicenter, international, open-label, randomized trial of adjuvant nab-paclitaxel plus gemcitabine (nab-P/G) *vs* gemcitabine for surgically resected pancreatic adenocarcinoma. J Clin Oncol 2019; 37 (15 suppl): 4000. doi.org/10.1200/JCO.2019.37.15-suppl.4000
26. Japan Pancreas Society. Clinical Practice Guidelines for Pancreatic Cancer 2019, Kanehara, Tokyo, Japan, 2019. (in Japanese)
27. Conroy T, Desseigne F, Ychou M, *et al*. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011; 364:1817-1825.
28. Von Hoff DD, Ervin T, Arena FP, *et al*. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013; 369:1691-1703.
29. Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, Lee JE, Pisters PW, Evans DB, Wolff RA. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol. 2006; 13:1035-46.
30. Isaji S, Mizuno S, Windsor JA, Bassi C, Fernández-Del Castillo C, Hackert T, Hayasaki A, Katz MHG, Kim SW, Kishiwada M, Kitagawa H, Michalski CW, Wolfgang CL. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018; 18:2-11.
31. Golcher H, Brunner TB, Witzigmann H, Marti L, Bechstein WO, Bruns C, Jungnickel H, Schreiber S, Grabenbauer GG, Meyer T, Merkel S, Fietkau R, Hohenberger W. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. Strahlenther Onkol. 2015; 191:7-16.
32. Casadei R, Di Marco M, Ricci C, Santini D, Serra C, Calculli L, D'Ambra M, Guido A, Morselli-Labate AM, Minni F. Neoadjuvant Chemoradiotherapy and Surgery Versus Surgery Alone in Resectable Pancreatic Cancer: A Single-Center Prospective, Randomized, Controlled Trial Which Failed to Achieve Accrual Targets. J Gastrointest Surg. 2015; 19:1802-1812.
33. Versteijne E, Suker M, Groothuis K, *et al*. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. J Clin Oncol. 2020; 38:1763-1773.
34. Motoi F, Kosuge T, Ueno H, Yamaue H, Satoi S, Sho M, Honda G, Matsumoto I, Wada K, Furuse J, Matsuyama Y, Unno M; Study Group of Preoperative Therapy for Pancreatic Cancer (Prep) and Japanese Study Group of Adjuvant Therapy for Pancreatic cancer (JSAP). Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). Jpn J Clin Oncol. 2019; 49:190-194.
35. Ettrich TJ, Berger AW, Perkhofer L, *et al*. Neoadjuvant plus adjuvant or only adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer - the NEONAX trial (AIO-PAK-0313), a prospective, randomized, controlled, phase II study of the AIO pancreatic cancer group. BMC Cancer. 2018; 18:1298.
36. Simionato F, Zecchetto C, Merz V, *et al*. A phase II study of liposomal irinotecan with 5-fluorouracil, leucovorin and oxaliplatin in patients with resectable pancreatic cancer: the nITRO trial. Ther Adv Med Oncol. 2020; 12:1758835920947969.
37. Labori KJ, Lassen K, Hoem D, Grønbech JE, Søreide JA, Mortensen K, Smaaland R, Sorbye H, Verbeke C, Dueland S. Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) - study protocol for a national multicentre randomized controlled trial. BMC Surg. 2017; 17:94.
38. Schwarz L, Vernerey D, Bachet JB, Tuech JJ, Portales F, Michel P, Cunha AS. Resectable pancreatic adenocarcinoma neo-adjuvant FOLF(IRIN)OX-based chemotherapy - a multicenter, non-comparative, randomized, phase II trial (PANACHE01-PRODIGE48 study). BMC Cancer. 2018; 18(1):762.
39. Alliance for Clinical Trials in Oncology. A Phase III Trial of Perioperative Versus Adjuvant Chemotherapy for Resectable Pancreatic Cancer. Clinical Trial Registration NCT04340141; clinicaltrials.gov. *https://clinicaltrials.gov/ct2/show/NCT04340141* (accessed May 23, 2022).
40. Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, Vauthey JN, Abdalla EK, Crane CH, Wolff RA, Varadhachary GR, Hwang RF. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008; 206:833-848.
41. Kato H, Usui M, Isaji S, Nagakawa T, Wada K, Unno M, Nakao A, Miyakawa S, Ohta T. Clinical features and treatment outcome of borderline resectable pancreatic head/body cancer: a multi-institutional survey by the Japanese Society of Pancreatic Surgery. J Hepatobiliary Pancreat Sci. 2013; 20:601-10.
42. Nagakawa Y, Sahara Y, Hosokawa Y *et al*. Clinical Impact of Neoadjuvant Chemotherapy and Chemoradiotherapy in Borderline Resectable Pancreatic Cancer: Analysis of 884 Patients at Facilities Specializing in Pancreatic Surgery. Ann Surg Oncol. 2019; 26:1629-1636.
43. Miyasaka Y, Nakamura M. ASO Author Reflections: Impact of Neoadjuvant Chemotherapy with Gemcitabine Plus Nab-Paclitaxel for Borderline Resectable Pancreatic Cancer on Surgical Outcomes. Ann Surg Oncol. 2019; 26(Suppl 3):739-740.
44. Janssen QP, Buettner S, Suker M, *et al*. Neoadjuvant FOLFIRINOX in Patients With Borderline Resectable Pancreatic Cancer: A Systematic Review and Patient-Level Meta-Analysis. J Natl Cancer Inst. 2019; 111:782-794.
45. Jang JY, Han Y, Lee H, *et al*. Oncological Benefits of Neoadjuvant Chemoradiation With Gemcitabine Versus Upfront Surgery in Patients With Borderline Resectable Pancreatic Cancer: A Prospective, Randomized, Open-label, Multicenter Phase 2/3 Trial. Ann Surg. 2018; 268:215-222.
46. Versteijne E, Suker M, Groothuis K, *et al*. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. J Clin Oncol. 2020; 38:1763-1773.
47. Ghaneh P, Palmer DH, Cicconi S, *et al.*, and European Study Group for Pancreatic Cancer (ESPAC). ESPAC-5F: Four-arm, prospective, multicenter, international randomized phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy

(CRT) in patients with borderline resectable pancreatic cancer. J Clin Oncol. 2020 38: 15_suppl, 4505-4505.
48. Suker M, Beumer BR, Sadot E, *et al*. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol. 2016; 17:801-810.
49. Sadot E, Doussot A, O'Reilly EM, Lowery MA, Goodman KA, Do RK, Tang LH, Gönen M, D'Angelica MI, DeMatteo RP, Kingham TP, Jarnagin WR, Allen PJ. FOLFIRINOX Induction Therapy for Stage 3 Pancreatic Adenocarcinoma. Ann Surg Oncol. 2015; 22:3512-3521.
50. Marthey L, Sa-Cunha A, Blanc JF, Gauthier M, Cueff A, Francois E, Trouilloud I, Malka D, Bachet JB, Coriat R, Terrebonne E, De La Fouchardière C, Manfredi S, Solub D, Lécaille C, Thirot Bidault A, Carbonnel F, Taieb J. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. Ann Surg Oncol. 2015; 22:295-301.
51. Bednar F, Zenati MS, Steve J, Winters S, Ocuin LM, Bahary N, Hogg ME, Zeh HJ 3rd, Zureikat AH. Analysis of Predictors of Resection and Survival in Locally Advanced Stage III Pancreatic Cancer: Does the Nature of Chemotherapy Regimen Influence Outcomes? Ann Surg Oncol. 2017; 24:1406-1413.
52. Lee J, Lee JC, Gromski MA, Kim HW, Kim J, Kim J, Hwang JH.Clinical outcomes of FOLFIRINOX in locally advanced pancreatic cancer: A single center experience. Medicine (Baltimore). 2018; 97: e13592.
53. Gemenetzis G, Groot VP, Blair AB, Laheru DA, Zheng L, Narang AK, Fishman EK, Hruban RH, Yu J, Burkhart RA, Cameron JL, Weiss MJ, Wolfgang CL, He J. Survival in Locally Advanced Pancreatic Cancer After Neoadjuvant Therapy and Surgical Resection. Ann Surg. 2019; 270:340-347.
54. Philip PA, Lacy J, Portales F, *et al*. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. Lancet Gastroenterol Hepatol. 2020; 5:285-294.
55. Bellon E, Gebauer F, Tachezy M, Izbicki JR, Bockhorn M. Pancreatic cancer and liver metastases: state of the art. Updates Surg. 2016; 68:247-251.
56. Frigerio I, Regi P, Giardino A, Scopelliti F, Girelli R, Bassi C, Gobbo S, Martini PT, Capelli P, D'Onofrio M, Malleo G, Maggino L, Viviani E, Butturini G. Downstaging in Stage IV Pancreatic Cancer: A New Population Eligible for Surgery? Ann Surg Oncol. 2017; 24:2397-2403.
57. Wright GP, Poruk KE, Zenati MS, Steve J, Bahary N, Hogg ME, Zuriekat AH, Wolfgang CL, Zeh HJ 3rd, Weiss MJ. Primary Tumor Resection Following Favorable Response to Systemic Chemotherapy in Stage IV Pancreatic Adenocarcinoma with Synchronous Metastases: a Bi-institutional Analysis. J Gastrointest Surg. 2016; 20:1830-1835.
58. Satoi S, Fujii T, Yanagimoto H, Motoi F, Kurata M, Takahara N, Yamada S, Yamamoto T, Mizuma M, Honda G, Isayama H, Unno M, Kodera Y, Ishigami H, Kon M. Multicenter Phase II Study of Intravenous and Intraperitoneal Paclitaxel With S-1 for Pancreatic Ductal Adenocarcinoma Patients With Peritoneal Metastasis. Ann Surg. 2017; 265:397-401.
59. Satoi S, Yamaue H, Kato K, *et al*. Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with 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.

Received June 4, 2022; Revised June 16, 2022; Accepted June 20, 2022.

**Address correspondence to:*
Yoshihiro Sakamoto, Department of Hepato-Biliary-Pancreatic Surgery, Kyorin University Hospital, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan.
E-mail: yosakamo@ks.kyorin-u.ac.jp

Released online in J-STAGE as advance publication June 23, 2022.