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

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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
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-fluourouracil (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 PAC 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.

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

| Author          | Year       | Procedure of extended resection | Number  | 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                  | 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 Distal gastrectomy | 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.
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.  | 2015 | Germany      | R             | GEM/Cisplatin+RT            | 33     | 19 (58)                | 52 vs. 48       | 17.4 vs. 14.4     |
|                 |      |              |               | Upfront surgery             |        | 23 (70)                | \( p = 0.81 \)  | \( p = 0.96 \)    |
| Casadei et al.  | 2015 | Italy        | R             | GEM+RT                      | 18     | 11 (61)                | 39 vs. 25       | 22.4 vs. 19.5     |
|                 |      |              |               | Upfront surgery             |        | 15 (75)                | \( p = 0.49 \)  | \( p = 0.97 \)    |
| Versteijine et al. | 2020 | Netherlands | R/BR          | GEM+RT                      | 119    | 72 (61)                | 71 vs. 40       | 16.0 vs. 14.3     |
|                 |      |              |               | Upfront surgery             |        | 92 (72)                | \( p < 0.001 \) | \( p = 0.096 \)   |
| Motoi et al.    | 2019 | Japan        | R/BR          | GEM+S-1                     | 182    | 140 (77)               | -              | 36.7 vs. 26.7     |
|                 |      |              |               | Upfront surgery             | 180    | 130 (72)               | \( p = 0.015 \) |                   |

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

### Table 5. Ongoing RCTs of neoadjuvant 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 |
| nTRO (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 1 year        |
| 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 (4, post 2) Adjuvant FOLFIRINOX (6) | 352    | OS                                 |

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

### 5. CS for UR-M PC

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

| Study                  | Design    | Country     | Regimen                      | Number | Primary endpoint          |
|------------------------|-----------|-------------|------------------------------|--------|---------------------------|
| ALLIANCENCT02839343    | Phase II  | USA         | FOLFIRINOX + FOLFIRINOX + SBRT | 112    | 1.5-year OS               |
| PANDAS-PRODIGE44       | Phase II  | France      | mFOLFIRINOX + Cape-base RT    | 92     | R0 resection rate         |
| GABANANCE trial        | Phase II/III | Japan     | GnP S-1 + RT                 | 110    | Phase II: R0 resection rate |

Cape: capecitabine, GEM: gemcitabine, GnP: gemcitabine plus nab-paclitaxel, mFOLFIRINOX: modified FOLFIRINOX, OS: overall survival, RT: radiation therapy, 5-FU: 5-fluorouracil.
Naohiro Okano has received honoraria from Taiho Pharmaceutical, Eli Lilly Japan, Eisai, Bayer Yakuhin, Chugai Pharma, Ono.

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). Satoh 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, Gemenetzis 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 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.

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

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

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