Yonago Acta Medica 2023;66(2):202–207 doi: 10.33160/yam.2023.05.014 *Review Article*

Current Value of Perioperative Therapies for Resectable or Borderline Resectable Pancreatic Cancer

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ABSTRACT

Invasive pancreatic ductal carcinoma is a representative refractory malignant tumor, and even with the development of early diagnosis and treatment techniques, the treatment outcome has been remarkably poor. Surgical resection is the curative treatment for resectable pancreatic cancer and borderline resectable pancreatic cancer. However, the survival rate in patients with pancreatic cancer treated by resection alone is low because of the high postoperative recurrence rate. In this review article, we report recent studies on perioperative treatment for pancreatic cancer. Perioperative therapy is the addition of chemotherapy or radiation therapy before or after surgery to improve resectability and curative effects. Because it is difficult to cure redsecttable pancreatic cancer by surgery alone, multidisciplinary treatment combined with perioperative adjuvant chemotherapy is the current standard of care. Although perioperative chemotherapy and chemoradiotherapy have been investigated for borderline resectable pancreatic cancer, the effectiveness of preoperative treatment has not been sufficiently proven. Potentially curative pancreatic cancer is treated by surgery plus perioperative therapy; treatment cannot be either alone. We regard the successful completion of surgery and perioperative care as the key to improving treatment outcomes. Therefore, ongoing randomized controlled trials for the treatment of BR-pancreatic cancer are expected to induce further improvements survival outcomes of patients with BR-pancreatic cancer.

Key words preoperative therapy; postoperative therapy; pancreatic cancer

Invasive pancreatic ductal carcinoma is a representative refractory malignant tumor, and even with the development of early diagnosis and treatment techniques, the treatment outcome has been remarkably poor. According to the 2020 edition of GLOBOCAN, pancreatic ductal adenocarcinoma is the 15th most common cancer worldwide, affecting 4.9 per 100,000 people and constituting 495,773 new cases.[1] Although radical surgical resection is the most effective treatment for pancreatic cancer, early diagnosis is still difficult, and the disease is often detected in unresectable advanced cases. The postoperative recurrence rate is high even after curative resection because micrometastases may already occur at surgery in most patients with pancreatic cancer, and the 5-year survival rate for pancreatic cancer treated by resection alone is only about 10%.[2, 3] Therefore, multidisciplinary treatment combined with perioperative adjuvant chemotherapy is the current standard of care.

Perioperative adjuvant chemotherapy is generally indicated for resectable pancreatic cancer (R-pancreatic cancer), but clinical trials also include partially borderline resectable (BR) pancreatic cancer. BR-pancreatic cancer is the most likely to have a histological remnant (R1) after upfront surgery alone, and it is classified by contact with or invasion of the portal vein (PV) or artery. According to the National Comprehensive Cancer Network guidelines, resectability status is classified using multidetector CT imaging. R-pancreatic cancer is defined as a clear fat plane around the celiac axis, hepatic artery, and superior mesenteric artery and no radiological evidence of distortion of the superior mesenteric vein (SMV) or PV and BR-pancreatic cancer. By contrast, BR-pancreatic cancer is defined as a venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement or radiographic findings encompassing a short segment of the hepatic artery with no evidence of tumor extension into the celiac axis and/or tumor attachment of < 180 degrees around the superior mesenteric artery.[4]

The importance of preoperative chemotherapy or preoperative chemoradiation for BR pancreatic cancer has been discussed; however, its efficacy in improving

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Received 2023 March 22
Accepted 2024 April 17
Online published 2023 May 10
Abbreviations: BR, borderline resectable; CI, confidence interval; GEM, gemcitabine; GnP, GEM + nab-paclitaxel; GS, gemcitabine plus S-1; HR, hazard ratio; MST, median survival time; OS, overall survival; PV, portal vein; R, resectable; RFS, recurrence-free survival; SMV, superior mesenteric vein.

the prognosis has not yet been demonstrated.

RESECTABLE PANCREATIC CANCER

Preoperative chemotherapy

The purpose of preoperative therapy is to provide a therapeutic intervention before surgery for targets that are not responsive to surgery alone. Radical surgery for pancreatic cancer, as represented by pancreaticoduodenectomy, is relatively invasive and has a high complication rate.[5] Postoperative complications or postoperative decline in the general condition can delay, reduce, interrupt, or preclude the initiation of adjuvant therapy. However, preoperative chemotherapy can be performed in patients in good general condition, allowing for higher dose-intensity treatment.

The Prep-02/JSAP-05 study was conducted to compare gemcitabine (GEM) plus S-1 (GS) therapy with upfront surgery in patients with R-pancreatic cancer in Japan.[6, 7] The median survival time (MST) was 36.7 months in the GS group and 26.6 months in the upfront surgery group [hazard ratio (HR), 0.72; 95% confidence interval (CI), 0.55–0.94; $P = 0.015$], showing a significant improvement in the prognosis. Grade 3/4 adverse events were observed in 72.8% of patients in the GS group, and most of these events were neutropenia and leukopenia. However, in patients who underwent resection, there were no significant differences in the operative time, intraoperative blood loss, or postoperative complication rates between the preoperative GS therapy group and the upfront surgery group. Based on the results of this study, preoperative GS therapy has been widely introduced for R-pancreatic cancer in Japan. Nevertheless, the study was limited to patients with pathologically confirmed pancreatic cancer, invasive cancer [those with noninvasive cancer (Tis) were excluded], age of 20 to 79 years, and a performance status of 0 or 1. With these factors in mind, it is important to be aware that preoperative chemotherapy was not recommended for all patients diagnosed with R-pancreatic cancer.

The SWOG S1505 trial compared regimens by using standard combination therapy [FOLFIRINOX vs. GEM + nab-paclitaxel (GnP)] for perioperative adjuvant therapy (preoperative and postoperative).[8, 9] The 2-year survival rate in the FOLFIRINOX arm was 41.6% (MST, 22.4 months), and that in the GnP arm was 48.8% (MST, 23.6 months). Therefore, the study concluded that neither regimen improved overall survival (OS) compared with the previous standard of care. The PREOPANC01 trial was a phase III study performed to evaluate the significance of preoperative chemoradiation in R- and BR-pancreatic cancer in the Netherlands.[10] This study showed that although there was a trend toward better OS in the preoperative treatment group, the difference was not significant. The study included about half of the total number of patients with BR-pancreatic cancer, which is insufficient evidence to provide clarity on the significance of treatment for R-pancreatic cancer. As a result, no preoperative chemotherapy is still recommended as standard treatment for patients with R-pancreatic cancer in Western countries.

Several trials regarding preoperative chemotherapy are still ongoing. The CSGO-HBP-015 trial is a phase II trial comparing GnP and GS as preoperative chemotherapy.[11] The primary endpoint is recurrence-free survival (RFS). The PREOPANC-3 study is a comparison of preoperative and postoperative treatment with FOLFIRINOX. The primary endpoint is 5-year OS. These results are expected to provide new evidence for preoperative chemotherapy for R-pancreatic cancer (Table 1).

Postoperative chemotherapy

Postoperative chemotherapy is a treatment administered after radical resection has been performed to eradicate residual tumor tissue at the cellular level, thereby improving the cure rate. As noted above, the complication rate is high after surgery for pancreatic cancer, so it is important that the patient progresses without postoperative complications and safely achieves postoperative chemotherapy. Stable postoperative chemotherapy with sufficient dose intensity has been shown to improve the prognosis after resection.[12] Preoperative treatment, surgery, and postoperative chemotherapy should be performed without delay to improve outcomes.

In Europe and elsewhere, a randomized phase III trial was conducted to compare GEM with surgery alone as adjuvant therapy after surgery for pancreatic cancer (CONKO-001).[3] The comparison of 6 months of GEM therapy versus resection alone confirmed a significant improvement in RFS and OS in the GEM group (median RFS, 13.4 vs. 6.7 months; HR, 0.55; 95% CI, 0.44–0.69; $P < 0.0001$ and MST, 22.8 vs. 20.2 months; HR, 0.76, 95% CI, 0.61–0.95; $P = 0.01$). A similar study was conducted in Japan (JSAP02), which also confirmed the usefulness of GEM therapy.[13] Based on these results, GEM therapy has become one of the standard postoperative chemotherapy regimens.

In Japan, the JASPAC01 trial was a phase III trial comparing S1 therapy as postoperative chemotherapy versus conventional standard therapy, the GEM regimen.[14] This study was a non-inferiority trial of S-1 to GEM, but it was terminated at the interim analysis because the S-1 group had extremely favorable results

Table 1. Recent studies on preoperative chemotherapy for resectable pancreatic cancer

	Year	Phase	Location	Stage	Regimen	Number of cases	Primary endpoint	MST	*P*-value
Prep-02/JSAP-05	2019	III	Japan	R/BR	US GS	180 182	OS	26.7 36.7	0.015
SWOG S1505	2020	II	–	R	FFX GnP	55 47	OS	22.4 23.6	–
PREOPANC	2020	III	Netherlands	R/BR	US GEM + RT	127 119	OS	14.3 16.0	0.096
CSGO-HBP-015	–	II	Japan	R/BR	GnP GS	100 (total)	PFS	–	–
PREOPANC-3	–	III	Netherlands	R	pre FFX + post FFX US + post FFX	378 (total)	OS	–	–

BR, Borderline Resectable; FFX, FOLFIRINOX; GEM, gemcitabine; GnP, gemcitabine + nab-paclitaxel; GS, gemcitabine + S-1; MST, median survival time; OS, overall survival; PFS, progression-free survival; R, Resectable; RT, radiotherapy; US, upfront surgery.

Table 2. Recent studies on postoperative chemotherapy for resectable pancreatic cancer

	Year	Phase	Location	Stage	Regimen	Number of cases	Primary endpoint	MST	*P*-value
JASPAC01	2016	III	Japan	R/BR	GEM S-1	193 192	OS	25.5 46.5	< 0.001
ESPAC-4	2017	III	4 countries in Europe	R/BR	GEM GEM + Capecitabine	366 364	OS	25.5 28.0	0.032
PRODIGE 24/ ACCORD 25/ CCTG PA 6	2018	III	France, Canada	R	GEM FFX	246 247	DFS	35.0 54.4	0.003
APACT	2019	III	Europe, USA, Korea, Canada	R	GEM GnP	434 432	DFS	36.2 40.5	0.045

BR, Borderline Resectable; DFS, disease-free survival; FFX, FOLFIRINOX; GEM, gemcitabine; GnP, gemcitabine + nab-paclitaxel; MST, median survival time; OS, overall survival; R, Resectable.

(MST, 46.5 vs. 25.5 months; HR, 0.57; 95% CI, 0.44–0.72; $P < 0.0001$). The ESPAC04 trial compared GEM alone with the combination of GEM and capecitabine.[15] The GEM and capecitabine group showed a significant improvement in OS (MST, 28.0 vs. 25.5 months; HR, 0.82; 95% CI, 0.68–0.98; $P = 0.032$).

FOLFIRINOX and GnP, which are usually used as standard treatments for metastatic pancreatic cancer, were also being investigated as possible postoperative chemotherapy. The PRODIGE 24/ACCORD 25/CCTG PA 6 trial compared modified FOLFIRINOX to GEM monotherapy in Western countries.[16] The primary endpoint, median RFS, was improved in the FOLFIRINOX group (21.6 vs. 12.8 months; HR, 0.58; 95% CI, 0.46–0.73; $P < 0.001$), and the secondary endpoint, OS, was also improved in the modified FOLFIRINOX group (54.4 vs. 35.0 months; HR, 0.64; 9% CI, 0.48–0.86; $P = 0.003$). The APACT trial compared GnP with GEM alone.[17] The primary endpoint was disease-free survival as judged by independent review, and the secondary endpoints were OS and safety. The 5-year OS rate, a secondary endpoint, was improved in the GnP arm (41.8 vs. 37.7 months; HR, 0.80; 95% CI, 0.68–0.95), but disease-free survival, the primary endpoint, was not significantly different (19.4 vs. 18.8 months; HR, 0.88; 95% CI, 0.73–1.06; $P = 0.183$). Therefore, the benefit of GEM plus nab-PTX as postoperative chemotherapy is not yet clear (Table 2).

Based on these trials, S-1 regimen in Japan, and modified FOLFIRINOX or GEM and capecitabine regimens in Western countries are recommended as the standard postoperative chemotherapy.[18, 19]

BORDERLINE RESECTABLE PANCREATIC CANCER

Preoperative chemotherapy

The importance of preoperative chemotherapy or preoperative chemoradiotherapy for BR-pancreatic cancer has been discussed because a high percentage of patients with BR-pancreatic cancer have residual cancer even after prior surgical resection, which may not be effective in prolonging survival.[20] However, the efficacy of preoperative treatment in improving the prognosis of BR-pancreatic cancer has not yet been established.

In a retrospective multicenter study, the prognoses of 704 patients with pancreatic head cancer who underwent upfront surgery with pancreaticoduodenectomy without preoperative chemotherapy were analyzed based on the National Comprehensive Cancer Network resectability classification. The MST was 25.7 months for R-pancreatic cancer and 22.0 months for R-pancreatic cancer with < 180 degrees of contact with the PV (i.e., R-PV pancreatic cancer). The MST was 25.7 months for R-pancreatic cancer and 22.0 months for R-PV pancreatic cancer, whereas BR-pancreatic cancer invading the PV (17.4 months) and BR-pancreatic cancer invading an artery (11.1 months) had a significantly poorer prognosis ($P < 0.001$). In addition, PV/SMV contact of > 180 degrees ($P = 0.008$) and arterial contact ($p < 0.001$) were independent prognostic factors.[21] In a retrospective study of BR-pancreatic cancer reported by the Japanese Society of Pancreatic Surgery, although the resection rate was significantly lower in the preoperative treatment group (75.1%) than in the upfront surgery group (93.3%) ($P < 0.001$), the R0 resection rate was significantly higher in the preoperative treatment group ($P < 0.001$). Furthermore, the MST was significantly better in the preoperative treatment group (25.7 months) than in the upfront surgery group (19.0 months) ($P = 0.015$), and it was also significantly better in the preoperative treatment group in the resected cases ($P < 0.001$). However, among the preoperative treatment groups, the MST in the preoperative chemotherapy group was 29.2 and 22.5 months in the preoperative chemoradiation group, which was not significantly different ($P = 0.130$).[22] Although other retrospective studies have been reported, the chemotherapy regimen and other factors have not been established; thus, the effectiveness of preoperative treatment has not been sufficiently proven for BR-pancreatic cancer.[23–29]

With respect to prospective studies, a multicenter randomized study comparing upfront surgery versus preoperative treatment in BR-pancreatic cancer was reported in 2018.[30] The preoperative treatment regimen was chemoradiation by GEM plus radiation (54 Gy), and the primary endpoint was the 2-year survival rate. The 2-year OS was 26.1% (MST, 12 months) in the upfront surgery group and 40.7% (MST, 21 months) in the preoperative treatment group, indicating the efficacy of preoperative treatment for BR-pancreatic cancer ($P = 0.028$). In the PREOPANC trial, although there was no significant difference in the primary endpoint (OS for R- and BR-pancreatic cancer), the subgroup analysis focusing on BR-pancreatic cancer showed that the MST was 17.6 months (preoperative treatment group) and 13.2 months (upfront surgery group), suggesting the efficacy of preoperative chemoradiation for BR-pancreatic cancer (HR, 0.62; 95% CI, 0.40–0.95; $P = 0.029$).[10] Ongoing trials for preoperative treatment of BR-pancreatic cancer include GnP versus radiation therapy with S-1 (GABARNANCE), FOLFIRNOX versus radiation therapy after FOLFIRNOX (Alliance A021501), and GnP versus FOLFIRINOX plus radiation added to each (NCT02241551); these are being conducted as comparative studies (Table 3).

Preoperative chemotherapy

All phase III trials in postoperative chemotherapy, namely the JASPAC01 trial, the ESPAC04 trial, and the PRODIGE 24/ACCORD 25/CCTG PA 6 trial, included patients with resected pancreatic cancer without regard for resectability classification; hence in patients with BR-pancreatic cancer as well as R-pancreatic cancer, recommended regimens of postoperative chemotherapy are S-1 in Asian counties, and modified FOLFIRINOX or GEM and capecitabine regimens in Western countries, respectively.

CONCLUSION

Perioperative chemotherapy has become the standard of care for resected pancreatic cancer. However, the treatment practice for pancreatic cancer between Asian and Western counties is difference. Therefore, it should be necessary to conduct the clinical studies to compare Asian regimen with Western regimen to clarify which regimens might be the optimal treatment in patients with resected pancreatic cancer. With respect to BR-pancreatic cancer, no consensus on the standard perioperative treatment, in particular preoperative chemotherapy, has been established in any countries. Ongoing randomized controlled trials for the treatment of BR-pancreatic cancer are expected to induce further improvements survival outcomes of patients with BR-pancreatic cancer.

Table 3. Recent studies on preoperative therapy for borderline resectable pancreatic cancer

	Year	Phase	Location	Stage	Regimen	Number of cases	Primary endpoint	MST	*P*-value
NCT01458717	2018	II/III	Korea	BR	US GEM+RT	23 27	OS	12.0 21.0	0.028
PREOPANC	2020	III	Netherlands	R/BR	US GEM + RT	127 119	OS	14.3 16.0	0.096
GABARNANCE	–	II/III	Japan	BR	GnP→Surgery→S-1 S-1→Surgery→S-1	110 (total)	OS	–	–
Alliance A021501	2022	II	USA	BR	FFX FFX + RT	54 56	OS	29.8 17.1	–
NCT02241551	–	II	USA	BR	GnP FFX	20 20	Safety and efficacy†	–	–

†Efficacy: pathological complete response and R0 resection. Safety: Grade 4 toxicity. BR, Borderline Resectable; FFX, FOLFIRINOX; GEM, gemcitabine; GnP, gemcitabine + nab-paclitaxel; MST, median survival time; OS, overall survival; R, Resectable; RT, radiotherapy; US, upfront surgery.

Acknowledgments: We thank Angela Morben, DVM, ELS, from Edanz (https://jp.edanz.com/ac), for editing a draft of this manuscript.

The authors declare no conflict of interest.

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