Review

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Trends in the treatment of advanced pancreatic cancer

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SUMMARY Pancreatic cancer (PC) has the poorest prognosis among digestive cancers; only 15-20% of cases are resectable at diagnosis. This review explores multidisciplinary treatments for advanced PC, emphasizing resectability classification and treatment strategies. For locally advanced unresectable PC, systemic chemotherapy using modified FOLFIRINOX and gemcitabine with albumin-bound paclitaxel is standard, while the role of chemoradiation is debated. Induction chemotherapy followed by chemoradiation may be a promising therapy. Conversion surgery after initial chemotherapy or chemoradiotherapy offers favorable survival, however criteria for conversion need further refinements. For metastatic PC, clinical trials using immune checkpoint inhibitors and molecular targeted therapies are ongoing. Multidisciplinary approaches and further research are crucial for optimizing treatment and improving outcomes for advanced PC.

Keywords pancreatic cancer, multidisciplinary treatment, conversion surgery

1. Introduction

Pancreatic cancer (PC) has the poorest prognosis among digestive cancers; only 15-20% of cases are resectable at diagnosis, whereas 30-40% are locally advanced and 50-60% involve distant metastases that are initially unresectable (*1*). In PC, resection is the only treatment that offers the possibility of a cure; however, long-term prognosis cannot be expected with resection alone. Therefore, multidisciplinary treatment is recommended. In this chapter, we review the multidisciplinary treatment for advanced PC.

2. Establishing the definition of resectability for PC

In the early 2000s, attempts were made to classify PC based on their resectability. The 2004 NCCN guidelines first categorized PC, and further objective classification based on the anatomical extension of computed tomography (CT) images was proposed by the M.D. Anderson Cancer Center in 2006 (*2*). All PCs were classified as resectable (R), borderline resectable (BR), or unresectable (UR) based on local extension and the presence or absence of distant metastasis. In 2016, the international consensus on the classification of BR PC was based on anatomical configurations on CT imaging (Table 1) (*3*). Currently, the treatment strategy for PC is determined by the resectability status at diagnosis, with a multidisciplinary treatment strategy being key to successful treatment.

3. Multidisciplinary treatment for UR-locally advanced (LA) PC

3.1. Chemotherapy and chemoradiation (CRT) for UR-LA PC

UR-LA PC accounts for 10-20% of all PCs (*2*). To achieve disease control, initial treatment typically consists of chemotherapy regimens such as modified FOLFIRINOX (mFFX) or gemcitabine and albumin-bound paclitaxel (GnP) (*4*). However, the role of radiation in UR-LA treatment remains controversial. Two randomized controlled trials of chemotherapy and CRT for UR-LA PC have been previously reported (Table 2) (*5,6*). There have been reports of chemotherapy significantly improving overall survival (OS) (median survival 13.0 months *vs.* 8.6 months, $p = 0.03$) (*5*) and significantly worsening OS (median survival 9.2 months *vs*. 11.1 months, $p = 0.017$) (*6*), and currently, there is no definitive conclusion on the superiority of chemotherapy and CRT. However, the chemotherapy regimens used in the chemotherapy groups of these two RCTs were both GEM alone, and there is a demand for better treatment outcomes for UR-LA PC with more potent chemotherapy regimens. The results of a randomized phase II trial (JCOG1407) comparing mFFX with GnP as a first-line treatment

Table 1. The international consensus on the classification of BR PC defined based on the anatomical configurations on computed tomography imaging

Resectable (R)	• SMV/PV: no tumor contact or unilateral narrowing • SMV/PV: no tumor contact or unilateral narrowing
Borderline resectable (BR)	Subclassified according to SMV/PV involvement alone or arterial invasion.
BR-PV (SMV/PV involvement alone)	• SMV/PV: tumor contact ≥ 180 or bilateral narrowing/occlusion, not exceeding the inferior border of the duodenum. • SMA, CA, CHA: no tumor contact/invasion
BR-A (arterial involvement)	• SMA, CA, CHA: no tumor contact/invasion • CHA: tumor contact without showing tumor contact of the PHA and/or CA. (The involvement of the aorta is categorized as unresectable. Presence of variant arterial anatomy is not taken into consideration)
Unresectable: UR	Subclassified according to the status of distant metastasis
Locally advanced (LA)	• SMV/PV: bilateral narrowing/occlusion, exceeding the inferior border of the duodenum. • SMA, CA: tumor contact/invasion of ≥ 180 degree. • CHA: tumor contact/invasion showing tumor contact/invasion of the PHA and/or CA. • Ao: tumor contact or invasion
Metastatic (M)	• Distant metastasis

SMV, superior mesenteric vein; PV, portal vein; SMA, superior mesenteric artery; CA, celiac artery; CHA, common hepatic artery; PHA, proper hepatic artery.

Table 2. Results of two RCTs comparing chemotherapy alone and chemoradiation for unresectable, locally advanced pancreatic cancer

Author	Country/Year	Regimen	Number of patients	Median PFS (months)	Median OS (months)
Chauffert *et al*.	France/2008	60Gy/30Fr and GEM *vs.* GEM alone	119	7.2 *vs*. 11.6, $p = 0.025$	8.6 *vs*. 13.0, $p = 0.03$
Loehrer *et al*.	USA/2011	50.4Gy/28Fr and GEM *vs.* GEM alone	71	6.0 *vs*. 6.7	11.1 *vs*. 9.2, $p = 0.017$

GEM, gemcitabine; PFS, progression-free survival; OS, overall survival.

for UR-LA PC were reported in 2023 in Japan. The 1-year OS was 77.4% (95% confidence interval [CI], 64.9-86.0) and 82.5% (95% CI, 70.7-89.9), median OS was 23.0 months (19.3-29.3) and 21.3 months (18.2-24.1), median progression-free survival (PFS) was 11.2 months (95% CI, 9.9-15.9) and 9.4 months (95% CI, 7.4-12.8), and response rate was 30.9% (95% CI, 19.1-44.8) and 57.1% (95% CI, 41.0-72.3) in the mFFX and GnP arms, respectively. The 1-year survival and response rates were better in the GnP group, whereas the median OS and PFS were better in the mFFX group (*7*). It is necessary to discuss how the results of this study can be integrated into clinical treatment strategies.

3.2. Induction chemotherapy before CRT for UR-LA PC

UR-LA PC may potentially have distant metastases, and administration of induction chemotherapy could allow the early identification of cases in which distant metastases emerge during the initial phase of treatment (*8*). Therefore, favorable treatment outcomes can be achieved by administering potent induction chemotherapy to control potential distant metastases, followed by local control through CRT. Table 3 shows the results of trials of induction chemotherapy before CRT (*9-12*).

In the LAP07 randomized clinical trial, no improvement in OS was observed after induction chemotherapy with a combination of GEM and erlotinib (*9*).

In a prospective multicenter phase II trial (LAPACT trial), in which six cycles of induction chemotherapy (GnP) were administered for UR-LA PC, 58% (62/107) of patients completed induction chemotherapy. The disease control rate using induction chemotherapy was 77.6%, and the response rate was 33.6%, both of which were considered favorable. Subsequent treatments included CRT in 17% (18/107) and surgery in 16% (17/107) of patients. The median OS was 18.8 months (*10*). In a phase II randomized trial (JCOG1106 trial) that evaluated the effectiveness of induction chemotherapy with GEM alone for 12 weeks before CRT with S-1, the median OS for the group that received induction chemotherapy with GEM alone prior to CRT with S-1 was 17.2 months, compared to 19.0 months for the group without induction chemotherapy, showing no significant difference (hazard ratio [HR] (95% CI), 1.255 (0.816-1.930)) (*11*). Takada *et al*. conducted a retrospective study of 45 patients with UR-LA PC, including 25 who received GnP therapy as induction chemotherapy and 20 who received chemotherapy alone (*12*). They reported that the CRT group had a better prognosis than the chemotherapy-

Table 3. Trials on induction chemotherapy before chemoradiation for unresectable, locally advanced pancreatic cancer

Author	Country	Year	Design	Induction chemotherapy regimen	Treatment after chemotherapy	Number of patients	Median PFS (months) CRT *vs.* CTx	Median OS (months) CRT *vs.* CTx
Hummel *et al.*	USA	2016	Phase III, RCT	GEM and Erlotinib or GEM alone	50Gy/30Fr and capecitabine	269	9.9 *vs.* 8.4, $p = 0.06$	15.2 *vs.* 16.5, $p = 0.83$
Philip *et al.*	International	2020	Phase II	GnP	GnP or CRT or surgery	107	10.9	18.8
Ioka *et al.*	Japan	2021	Phase II, RCT	GEM	50.4Gy/28Fr and S-1	100	10.1 *vs.* 10.4, HR (95% CI) = 1.034 (0.689-1.551)	19 *vs.* 17.2, HR (95% CI) = 1.255 (0.816-1.930)
Takada *et al.*	Japna	2021	Retrospective	GnP	60Gy/25fr and GEM or S-1	45	17.9 *vs.* 7.6, $p = 0.044$	29.2 *vs.* 17.4, $p < 0.001$

RCT, randomized controlled trial; GEM, gemcitabine; GnP, gemcitabine and nab-paclitaxel; CRT, chemoradiation therapy; NA, not applicable; CTx, chemotherapy; HR, hazard ratio.

alone group (OS 29.2 months *vs.* 17.4 months, $p < 0.001$). It is expected that by administering CRT during a potent chemotherapy regimen, in addition to local control achieved through CRT, there will be a reduction in the adverse events associated with chemotherapy or an extension of the time until these events worsen. Therefore, it is necessary to accumulate evidence on the efficacy of induction chemotherapy with potent chemotherapeutic regimens.

3.3. Conversion surgery (CS) for UR-LA PC

Surgical resection of initially UR PC after remission following chemo(radio)therapy is defined as CS.

The rate of CS for UR-LA PC varied according to previous reports. A meta-analysis of 13 trials of FFX for UR-LA PC reported that 91 of 325 patients (28%) underwent CS, achieving 74% R0 resection (*13*). In a retrospective study of 454 cases in which mFFX or Gemcitabine GnP was administered for UR-LA PC, 38 patients (16%) underwent CS, achieving 89% R0 resection. The independent prognostic factors were normalized CA19-9 concentration, modified Glasgow prognostic score of 0, tumor shrinkage after chemotherapy, chemotherapy duration ≥ 8 months, and resection (*14*). In a study of patients who underwent CS for UR-LA PC, Nagai *et al.* reported that the prognosis was significantly better and the time to postoperative recurrence was significantly longer in cases where all three tumor markers (CA19-9, CEA, and DUPAN-2) were at normal levels preoperatively than in cases with elevated preoperative tumor markers (*15*). CS for UR-LA PC requires further accumulation of evidence regarding the criteria and timing for considering resection in the future.

4. Case

A 56-year-old woman was diagnosed with UR-LA pancreatic head cancer involving the common hepatic artery (CHA) (Figure 1A) and portal vein (PV) (Figure 1B). The patient underwent 19 courses of GnP therapy. Postchemotherapy CT revealed tumor shrinkage (Figure 2A) and regression of the soft tissue shadow around the CHA (Figure 2B). Additionally, CA19-9 levels decreased from 9880 U/mL to 800 U/mL after chemotherapy. It was determined that technical and oncological R0 resections were feasible. Subtotal stomach-preserving pancreaticoduodenectomy with CHA resection and reconstruction using the splenic artery and PV resection and reconstruction using a left renal vein graft were performed (Figure 3A, 3B). The operating time was 13 h and 34 min, with an intraoperative blood loss of 756 mL. The postoperative course was uneventful, and the patient was discharged on the 18th postoperative day. The patient has achieved recurrence-free survival for 10 months postoperatively.

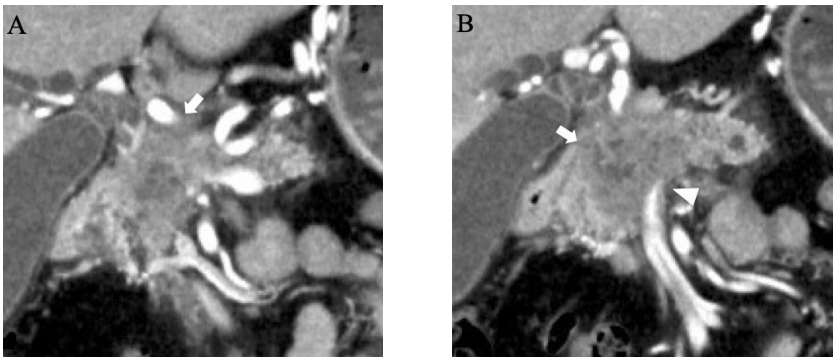

Figure 1. CT scan before chemotherapy. (A) Hepatobiliary and Pancreatic Oncology Group of Japan Clinical Oncology Group (JCOG). A randomized phase II study of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel for locally advanced pancreatic cancer (JCOG1407). **(B)** The arrow indicates a hypo-vascular mass in the head and body of the pancreas. The arrowhead points to suspected invasion of the tumor into the portal vein.

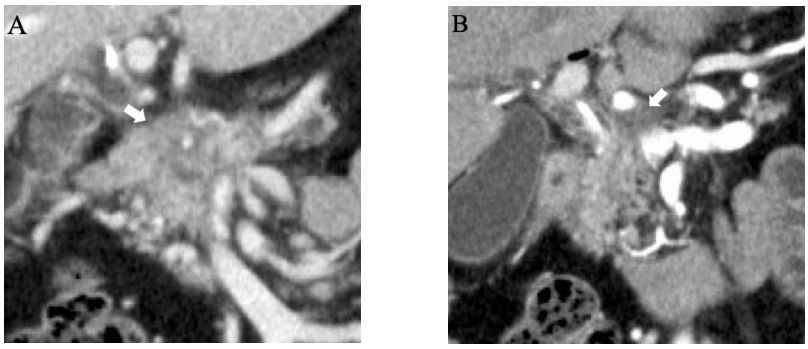

Figure 2. Preoperative CT scan. (A) After chemotherapy, the tumor has shrunk (arrow). **(B)** The low-density area around the CHA remains after chemotherapy (arrow).

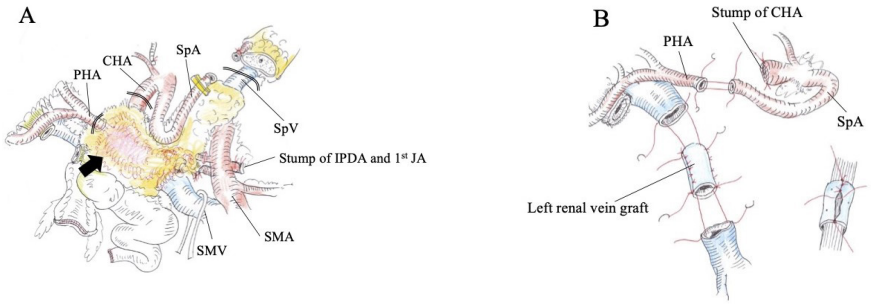

Figure 3. Operation record. (A) The tumor in the head and body of the pancreas (arrow) had invaded from the common hepatic artery (CHA) to the proper hepatic artery (PHA). The PHA, CHA, and portal vein were resected en bloc along with the tumor. The double lines indicate the sites of vascular transection. CHA, common hepatic artery; PHA, proper hepatic artery; SpA, splenic artery; SpV, splenic vein; SMV, superior mesenteric vein; SMA, superior mesenteric artery; IPDA, inferior pancreaticoduodenal artery; 1st JA, 1st jejunal artery. **(B)** In the arterial reconstruction, the splenic artery was anastomosed to the proper hepatic artery. A left renal vein graft was used for portal vein reconstruction. CHA, common hepatic artery; PHA, proper hepatic artery; SpA, splenic artery.

5. Multidisciplinary treatment for UR-metastasis (M) PC

5.1. Immune checkpoint inhibitors for UR-M PC

In immunotherapy, CD8+ T cells are the primary agents that induce tumor shrinkage. The tumor microenvironment within tumor tissues can be broadly classified into "hot (inflamed)" and "cold (non-inflamed)" based on the presence or absence of tumor-infiltrating lymphocytes, respectively, including CD8+ T cells. Hot tumors have a higher response rate to immune checkpoint inhibitors (*16*). PC is known to contain a large number of stromal components that result in poor infiltration of T cells (cold tumors) and a low tumor mutational burden. Consequently, PC respond poorly to immune checkpoint inhibitors. Furthermore, the abundance of stromal components in PC may impede drug delivery, potentially hindering the antitumor effects of cytotoxic chemotherapy and immune checkpoint inhibitors. Currently, the development of immune checkpoint inhibitors with antitumor effects is in progress. Table 4 shows the results of clinical trials of immune checkpoint inhibitors

as monotherapy or combination therapy (*17-19*).

In a phase II trial of ipilimumab (anti-CTLA-4), 27 patients were enrolled (UR-M PC, 20; UR-LA PC, 7), and tumor shrinkage was observed in three patients, but the response rate was 0% (*17*).

In a phase I trial of BMS-936559 (anti-PD-L1 antibody), 207 patients were enrolled, including 14 patients with PC. No response was reported in PC; however, response rates for malignant melanoma, non-small cell lung cancer (squamous cell carcinoma), non-small cell lung cancer (non-squamous cell carcinoma), mesothelioma, and renal cell carcinoma were 17%, 8%, 11%, 6%, and 12% respectively (*18*).

In a randomized phase II trial for patients with metastatic PC, the combination therapy of durvalumab (anti-PD-L1 antibody) and tremelimumab (anti-CTLA-4) was compared with Durvalumab alone; 32 patients were enrolled in the combination therapy group, and 33 patients in the Durvalumab alone group. Response rates were 3.1% and 0%, respectively. There was no difference in the median PFS and median OS (*19*).

These findings indicated that immune checkpoint inhibitors alone are not effective against PC. In the future, it will be necessary to evaluate biomarker expression to identify patients most likely to benefit from immune checkpoint inhibitors.

5.2. Combination of immune checkpoint inhibitors and cytotoxic chemotherapy for UR-M PC

Clinical trials are currently being conducted to evaluate the efficacy of combination therapies using immune checkpoint inhibitors and cytotoxic anticancer drugs. Table 5 summarizes the main results of the clinical trials (*20-24*).

Thirty-eight patients were enrolled in a phase I trial of combination therapy with tremelimumab (anti-CTLA-4) and GEM for PC with distant metastases that had not been previously treated with chemotherapy. Among the 28 patients in whom efficacy could be evaluated, two (7.1%) showed a response, and the median OS was 7.4 months (*20*).

A phase Ib/II trial targeting solid tumors was conducted using combination therapy with pembrolizumab and GnP. Seventeen patients were enrolled in this PC cohort study. Twelve (70.6%) patients received first-line treatment. The response rate, median PFS, and median OS were 27.3%, 9.1 months, and 15.0 months, respectively (*21*).

A phase Ib trial of combination therapy with ipilimumab (anti-CTLA-4) and GEM for advanced PC enrolled 21 patients (UR-M PC, 20; UR-LA PC, 1). Eleven patients (52%) received second-line treatment, and three patients (14%) received third-line treatments. The response rate, median PFS, and median OS were 14%, 2.78 months, and 6.90 months, respectively (*22*).

Table 4. Results of clinical trials on immune checkpoint inhibitors as monotherapy or combination therapy for unresectable metastatic pancreatic cancer

Author	Year	Country	Design	Regimen	Number of patients	Response rate	Median PFS (95% CI)	Median OS (95% CI)
Royal *et al.*	2010	USA	Phase II	Ipilimumab	27	0%	NA	NA
Brahmer *et al.*	2012	USA	Phase I	BMS-936559	14	0%	NA	NA
O'Reilly *et al.*	2019	USA	Phase II, RCT	Durvalumab *vs.* Durvalmab and Tremelimumab	65	0% *vs.* 3.1%	1.5 months (1.3-1.5 months) *vs.* 1.5 months (1.2-1.5 months)	3.6 months (2.7-6.1 months) *vs.* 3.1 months (2.2-6.1 months)

PFS, progression-free survival; OS, overall survival; RCT, randomized controlled trial; NA, not applicable.

Table 5. Clinical trials on a combination of immune checkpoint inhibitors and cytotoxic chemotherapy for unresectable metastatic pancreatic cancer

Author	Year	Country	Design	Regimen	Number of patients	Response rate	Median PFS (months)	Median OS (months)
Aglietta *et al.*	2014	Italy	Phase I	Tremelimumab and GEM	38	7.1%	NA	7.4
Weiss	2019	USA	Phase Ib/II	Pembrolizumab and GnP	17	27.3%	9.1	15
Kamath *et al.*	2020	USA	Phase Ib	Ipilimumab and GEM	21	14%	2.78	6.9
Renouf *et al.*	2022	Canda	Phase II	Durvalumab and tremelimumab and GnP *vs.* GnP	180	30.3% *vs.* 20.0%	5.5 *vs.* 5.4, $p = 0.91$	9.8 *vs.* 8.8, $p = 0.72$
Fu *et al.*	2023	China	Phase II, RCT	Sintilimab and mFFX *vs.* mFFX	110	50.0% *vs.* 23.9%	5.9 *vs.* 5.7, $p > 0.05$	10.9 *vs.* 10.8, $p > 0.05$

PFS, progression-free survival; OS, overall survival; RCT, randomized controlled trial; GEM, gemcitabine; GnP, gemcitabine and nab-paclitaxel; mFFX, modified FOLFIRINOX.

A randomized phase II trial (CCTG PA.7 trial) was conducted to assess the additive effects of durvalumab and tremelimumab on GnP as a first-line treatment for PC with distant metastases. A total of 119 and 61 patients were allocated to the four-drug combination and GnP groups, respectively. The primary endpoint, median OS, was 9.8 months in the four-drug combination group and 8.8 months in the GnP group (HR: 0.94, 90% CI: 0.71-1.25), showing no additive effects of durvalumab and tremelimumab. The response rate and median PFS were 30.3% and 5.4 months, respectively, in the four-drug combination group compared to 23.0% and 5.4 months, respectively, in the GnP group (*23*).

A randomized phase II trial (CISPD3 trial) was conducted to assess the additive effect of sintilimab on mFFX in PC with distant metastases that had not been treated with chemotherapy or developed resistance to gemcitabine-based first-line treatment. A total of 55 patients were enrolled in each group. The primary endpoint, median OS, was 10.9 months in the sintilimab and mFFX combination group compared to 10.8 months in the mFFX group (HR: 1.07, 95% CI: 0.69-1.68), showing no additive effect of sintilimab. However, the response rates and median PFS were 50.0% and 5.9 months in the sintilimab and mFFX combination group, respectively, and 23.9% and 5.7 months, respectively, in the mFFX group, with a significant difference in the response rates (*24*).

Cytotoxic anticancer drugs are expected to enhance the effects of immune checkpoint inhibitors. However, the results of these clinical trials showed that the effectiveness of gemcitabine alone, GnP, and mFFX therapies remained unchanged, and no additive effect of immune checkpoint inhibitors on cytotoxic chemotherapy was observed in PC.

5.3. Molecular targeted therapy for UR-M PC

Few molecular targeted therapies have shown efficacy against PC. However, in recent years, promising therapeutic target proteins have been identified for PC, and their development is progressing.

A randomized phase III trial (NCIC CTG PA.3 trial) comparing GEM and placebo therapy with GEM and erlotinib combination therapy for PC with local advancement or distant metastases enrolled 569 patients. The final analysis was conducted after observing 486 deaths, and the primary endpoint, OS, was significantly better in the erlotinib combination group (HR: 0.82, 95% CI: 0.69-0.99, $p = 0.038$). However, in the erlotinib combination group, there were more adverse events, including rash in 72% of patients and interstitial lung disease in 2.1% (*25*).

In a randomized phase III (POLO trial), that assessed the efficacy of the PARP inhibitor olaparib in patients with unresectable PC and germline BRCA gene mutations, 154 patients were enrolled. The patients were allocated to the olaparib and placebo groups in a 3:2 ratio. The primary endpoint, median PFS, was 7.4 months for the olaparib group compared to the placebo group, with an HR of 0.53 (95%CI 0.35-0.82, $p < 0.001$), demonstrating the superiority of maintenance therapy with olaparib (*26*).

In recent years, promising therapeutic target proteins for PC have been discovered and new targeted therapies are currently under development.

The development of drugs targeting CLDN18.2 is underway. CLDN18.2 is selectively expressed in tight junctions of the stomach and pancreas. In normal cells, it is located within tight junctions, making it difficult for anti-CLDN18.2 antibodies to reach it, even if they are present in the bloodstream. In contrast, cancer cells exhibit disrupted cell polarity, allowing antibody drugs to bind to CLDN18.2. Zolbetuximab is a monoclonal IgG1 antibody that binds to CLDN18.2, and induces cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In the SPOTLIGHT (*27*) and GLOW (*28*) trials targeting unresectable advanced gastric cancer, combination therapy with cytotoxic anticancer drugs and zolbetuximab was shown to be significantly superior in terms of OS. Against this background, a randomized phase II trial (NCT03816163) is underway to compare combination therapy of zolbetuximab and GnP with GnP therapy alone in patients with PC with distant metastases and high CLDN18.2 expression.

Results from phase I/II trials of sotorasib and adagrasib, antibody drugs targeting the KRAS p.12C mutant protein, have been reported.

In a single-arm Phase II trial targeting KRAS G12C-mutated advanced PC, 38 patients received sotorasib. The objective response rate was 21%, median PFS was 4.0 months, and median OS was 6.9 months (*29*).

In a phase I/II trial (KRYSTAL-1 trial) targeting KRAS G12C-mutant solid tumors, 12 of 42 patients with PC were administered adagrasib. The objective response rate, disease control rate, and median PFS was 50.0%, 100%, and 6.6 months, respectively (*30*). Among KRAS mutations other than KRAS G12C, drugs that can bind to the G12D mutation are also being developed and phase I clinical trials are being conducted (NCT05382559).

5.4. CS for UR-M PC

There are few reports of CS for PC with synchronous metastases, which included only selected patients and had poor prognoses after surgery with an approximately 10-month median OS (*31*). A small number of patients responded remarkably well to the novel chemotherapy approach, and metastatic tumors were no longer detectable on imaging studies. Table 6 shows the CS results for UR-M (liver) PC (*32-35*).

Frigerio *et al.* (*32*) administered chemotherapy to patients with PC with liver-only metastases and

Table 6. Results of clinical trials on conversion surgery for unresectable pancreatic cancer with liver metastasis

Author	Year	Country	Design	Regimen	Number of patients	Response rate	Median PFS (months)	Median OS (months)
Frigerio *et al*.	2022	Italy	Retrospective	FFX/GnP/GEM	52	86.5	23.9	37.2
Bachellier *et al*.	2022	France	Retrospective	FFX	92	50	5.4	12.7
Satoi *et al*.	2023	Japan	Retrospective	Multi regimen	10	NA	7.8	20.9
Takeda *et al*.	2023	Japan	Retrospective	mFFX/GnP/S-IROX	13	100	14.0	54.6

FFX, FOLFIRINOX; mFFX, modified FOLFIRINOX: GnP, gemcitabine and nab-paclitaxel; S-IROX, S-1 and Irinotecan, PFS, progression-free survival; OS, overall survival; NA, not applicable.

investigated the prognosis of 52 patients who achieved complete regression of the metastatic component and underwent pancreatectomy. The authors reported a median OS of 23.0 months.

Bachellier *et al.* (*33*) reported that a median OS of 92 patients with PC and synchronous liver metastases who underwent resection after neoadjuvant chemotherapy was 18.26 months.

Satoi *et al*. (*34*) reported a comparative study of patients with PC and synchronous liver metastases (n = 49), including those who underwent CS (n = 10), upfront surgery with or without short-term neoadjuvant chemotherapy for oligometastases and occult metastases limited to the liver (n = 8), and chemotherapy for R or BR diseases with occult liver-only metastases (n = 31). The median survival time from the initial treatment was significantly better in the CS group, (36.7 months) than in the other two groups. Additionally, CS was the only significant independent prognostic factor in the total cohort (HR, 0.173; p = 0.002). Takeda *et al.* (*35*) reported that patients with oligometastasis to the liver had a favorable survival duration of 13.2 months, which was significantly better than 8.2 months of patients with polymetastasis to the liver. The former group underwent CS more frequently than the latter (12% *vs.* 1.3%), and the MST in patients who underwent CS was 54.6 months.

alone; however, the criteria for performing CS vary between institutions.

Furthermore, it must be considered that CS is more challenging than standard pancreatic resection and carries a higher risk of postoperative severe complications (23% and 40.2%, respectively) (*33 35*).

6. Conclusion

Despite these improvements, PC continues to pose substantial challenges owing to its poor prognosis and high rate of initially unresectable cases. Multidisciplinary approaches incorporating potent chemotherapy regimens, chemoradiation, and innovative strategies, such as immune checkpoint inhibitors and molecular targeted therapies, are being explored to improve outcomes. CS has shown promise in patients with initially UR-LA or M PC, achieving notable survival benefits. However, the criteria and timing of CS require further investigation to optimize patient selection and outcomes.

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