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REVIEW ARTICLE

Conversion surgery for initially unresectable pancreatic cancer: current status and unresolved issues

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Abstract

Pancreatic cancer is one of the most lethal of all malignancies. One of the reasons for the dismal prognosis is that most diagnoses are made when the disease is either locally advanced or metastatic. Recent advances in chemotherapy and chemoradiotherapy (CRT) enable "conversion surgery" to be performed for selected patients with initially unresectable pancreatic cancer following favorable responses to preoperative treatment. Using FOLFIRINOX as preoperative treatment, the resection rate was reported as 6–44% of patients with locally advanced cancer and the prognosis of these patients was favorable. Even for metastasized cancer, recent reports show the effectiveness of conversion surgery, which has achieved 27–56 months of median overall survival. However, there are many unanswered questions about conversion surgery. The optimal regimen and duration of preoperative treatment remain unclear and there is still debate regarding the safety and effectiveness of vascular resection, which is often required for curative resection of locally advanced cancer. Accumulation of more data on conversion surgery is required to establish the safety and effectiveness of this treatment. In this review, we summarize the current status and unresolved issues about conversion surgery for initially unresectable pancreatic cancer.

Keywords Conversion surgery · Unresectable pancreatic cancer · Preoperative therapy

Introduction

Pancreatic cancer is the fourth-leading cause of cancer death in Japan, where pancreatic cancer is diagnosed in about 39,800 people and 34,000 will die of the disease each year [1]. In the US, pancreatic cancer is also the fourth-leading cause of cancer-related death [2] and is predicted to become the second-leading cause of cancer-related death by the end of this decade [3]. This is not only because of its rising incidence, but also because of its poor clinical outcomes. Although survival has improved for most malignancies, advances in treatments for pancreatic cancer have been slow and the 5-year overall survival rate remains at 7–8% in both the United States and Japan [1, 2].

Surgical resection gives the only hope for cure of this disease. A clinical trial comparing surgical resection and chemoradiotherapy (CRT) for localized pancreatic cancer invading the surrounding vasculature showed that patients who underwent surgical resection survived significantly longer than those treated with CRT alone. Moreover, the only long-term survivors were patients who underwent surgical resection [4]. However, the disease is usually diagnosed at an advanced stage, when it is either locally advanced or metastatic, so only 10–20% of patients are candidates for surgical resection [5]. Since the introduction of gemcitabine as a chemo-reagent for pancreatic cancer treatment [6], there has been much focus on establishing new chemotherapy protocols and the prognosis has improved. However, the survival benefit is still limited, with a 2-year survival rate of less than 10% [7, 8].

With this background, multidisciplinary treatments combining surgical resection and chemo- or chemoradiation therapy [C(R)T] have been applied to improve the survival of patients with pancreatic cancer and adjuvant therapy has become standard for patients who undergo surgical resection [9–11]. Many recent reports show the effectiveness of neoadjuvant therapy [12]. Moreover, surgical resection can be achieved in selected patients with initially unresectable

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pancreatic cancer after a favorable response to C(R)T; however, the effectiveness of surgical resection following C(R)T for initially unresectable pancreatic cancer remains unclear. In this review, we summarize the recent progress of surgical resection for both locally advanced and metastatic unresectable pancreatic cancer following preoperative C(R)T.

Definition of conversion surgery

In the review, "conversion surgery" is defined as "surgical resection following C(R)T for pancreatic cancer which is initially diagnosed as unresectable". Many words have been used to describe this treatment strategy. "Adjuvant surgery" [13, 14] or surgical resection after "neoadjuvant therapy" or "preoperative therapy" [15, 16] are also terms for such treatment. To emphasize the importance of surgical resection on survival, we think "conversion surgery", which is often used for the resection of advanced metastatic liver tumors after favorable chemotherapy response, is the most accurate term.

Recent advances in C(R)T

Patients with pancreatic cancer that would be difficult to resect are usually treated with chemotherapy; however, pancreatic cancer is known to be one of the most chemoresistant malignancies. Gemcitabine is the first chemotherapeutic agent found to be effective against pancreatic cancer. In 1997, Burris et al. reported the survival benefit of gemcitabine treatment vs. 5-FU for patients with advanced pancreatic cancer [6]. Since then, gemcitabine has been used globally as a standard chemotherapeutic agent for pancreatic cancer, but the response rate of gemcitabine treatment was limited to less than 10%. Because of this limited response, conversion surgery was performed for only a limited number of patients in the early 2000s.

In the GEST study, which compared gemcitabine plus S-1, S-1 alone, and gemcitabine alone, in patients with locally advanced and metastatic pancreatic cancer, the gemcitabine and S-1 combination therapy showed the highest response rate of 29.3% within three regimens, although the survival benefit did not reach statistical difference [17]. Recent new chemotherapies also show high response rates. In 2011, Conroy et al. [7] reported the survival advantage of FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin) vs. gemcitabine alone for patients with metastatic pancreatic cancer (ACCORD 11 trial). In this clinical trial, the response rate of FOLFIRINOX was 31.6%. A recent cohort study and systematic review also showed a favorable response rate and survival benefit even for patients with locally advanced cancer [18, 19]. In the MPACT trial, which showed the survival benefit of gemcitabine and albumin-bound paclitaxel combination (GnP) vs. gemcitabine alone for metastatic pancreatic cancer, the response rate in the GnP-treated patients was 23%, being higher than the 7% in the gemcitabine monotherapy-treated patients [8]. Those chemotherapy regimens also showed a very high response rate of 38.9% with FOLFIRINOX [20] and 58.8% with GnP [21] in phase II trials of Japanese patients. In line with these advances in chemotherapy, the number of reports on conversion surgery is increasing.

For locally advanced cancer, radiation therapy combined with systemic chemotherapy is also recommended in the NCCN [22] and Japanese guidelines [23]. In the 1990s, the combination of 5-FU and radiation was examined, but not widely accepted because of the limited survival benefit and high incidence of complications. In Japan, the combination of S-1 and radiation was studied in several prospective phase II trials and showed favorable survival with a median survival time of 14.3–16.8 months [24–26]. Despite these advances in CRT, tumor progression with rapid appearance of distant metastasis occurs in some patients. For these patients treated with radiation therapy, induction chemotherapy using gemcitabine-based chemotherapy before the radiation therapy has been helpful for patient selection and survival in several phase II studies [27, 28].

New radiation techniques also have been developed. Recent advances in the delivery and guidance of radiation, such as image-guided stereotactic body radiotherapy (SBRT) and intensity-modulated radiotherapy (IMRT), have offered the possibility of an escalating dose to a target with a lower dose to adjacent organs. These therapies were also introduced for locally advanced pancreatic cancer [29, 30]. Carbon ion radiation (CIR) offers a more conformal dose distribution to the target and a better biological effect because of its higher linear energy transfer than photon radiation. CIR is also used for locally advanced pancreatic cancer. According to a recent multi-institutional retrospective study in Japan, the median overall survival of patients with locally advanced pancreatic cancer treated with CIR was 21.5 months [31].

A recent LAP-07 trial comparing chemotherapy and CRT for locally advanced pancreatic cancer failed to show any survival benefit of CRT [32]. However, CRT showed decreased local progression rate and no increase in grade 3 and 4 toxicities. This result may indicate that CRT is useful for conversion surgery. Based on these results, a wide variety of C(R)T has been used against locally advanced pancreatic cancer.

Conversion surgery

With the progress of C(R)T, multidisciplinary treatment combining surgical resection and C(R)T has been widely accepted. Since the early 2000s, the number of reports on the

effectiveness of neoadjuvant/preoperative therapy for pancreatic cancer has been increasing. Gillen et al. [33] reported a systematic review and meta-analysis of preoperative/neoadjuvant therapy for pancreatic cancer, analyzing 111 studies including 4394 patients. They reported that surgical resection following neoadjuvant/preoperative therapy was performed in 33.2% of patients with non-resectable (including borderline resectable (BR) and unresectable (UR)) pancreatic cancer and the median survival of these patients was 20.5 months, which was better than that of patients who did not undergo resection. Surprisingly, this survival time was within the range of patients who were treated with primary resection and adjuvant therapy for resectable cancer (20.1–23.6 months).

Satoi et al. [13] reported the results of a multicenter survey focusing on the surgical resection of initially unresectable pancreatic cancer. This study included 58 cases, including 41 of locally advanced cancer and 17 of metastatic cancer. The median survival time of all 58 patients was 39.7 months. These reports showed clearly that there are certain patients who benefit from conversion surgery. However, there are several limitations to demonstrating the efficacy of conversion surgery. The analysis included both locally advanced and metastatic cancer, which might have different characteristics. Moreover, the criteria for surgical resection after preoperative therapy varies among institutions and C(R)T regimens for conversion surgery differ, making a meta-analysis very difficult. Thus, next we discuss recent trends regarding conversion surgery for locally advanced and metastatic pancreatic cancer, separately.

For locally advanced cancer

There are an increasing number of reports on conversion surgery for locally advanced pancreatic cancer since the 2010s, especially from high-volume centers. In the recent National Comprehensive Cancer Network (NCCN) guidelines (from Version 1.2018) [22], surgical resection of locally advanced cancer is a second-line therapy option for patients with good performance status and disease response after first-line therapy.

Bickenbach et al. from the Memorial Sloan-Kettering Cancer Center (NY, USA) [34] reported an analysis of 36 patients with initial stage III disease, in which the tumor invaded the surrounding major arteries such as the supramesenteric artery (SMA) or celiac artery (CEA), using a prospectively corrected database in their institute. The median overall survival of these patients was 25 months from surgery and 30 months from treatment initiation. Surprisingly, there was no difference in overall survival from the time of resection between these patients and case-matched patients who had initially resectable disease. Strobel et al. from the University Hospital Heidelberg (Germany) [16] also reported the results of an analysis of 257 patients undergoing surgery for initial locally advanced pancreatic cancer after C(R)T, using their prospective database. Of the total 257 patients, 120 (46.7%) underwent resection, with R0 in 42, R1 in 61, and R2 in 16. The median survival time was significantly longer for patients who underwent resection (13 months) than for those who underwent exploration (9 months). Notably, it was longest for patients who underwent R0 resection (25 months). These initial reports indicate that conversion surgery might extend the survival of patients with initially locally advanced unresectable pancreatic cancer, even in the era of gemcitabine-based chemotherapy,

Preoperative treatment using FOLFIRINOX

Since the introduction of FOLFIRINOX and GnP therapy for pancreatic cancer treatment, these regimens have been used as preoperative or neoadjuvant therapy. In 2015, Ferrone et al. [35] reported their primary experience of 40 patients who underwent resection following neoadjuvant treatment using FOLFIRINOX for locally advanced UR or BR cancer. They achieved an extremely high R0 resection rate of 92%. Moreover, four of these patients had minimal (< 1mm) and two had no evidence of cancer on pathologic examination. The median overall survival was 34 months, although the follow-up time was limited (median, 13 months).

Based on these favorable results, especially since 2015, several papers have been published on the effectiveness of neoadjuvant therapy using FOLFIRINOX for initially UR or BR pancreatic cancer. Reports including 10 or more cases of conversion surgery for unresectable locally advanced cancer were selected from a Pubmed search and are summarized in Table 1 [35–48]. Many of these papers report the combined results of locally advanced UR and BR cancer. In most of the studies, radiation therapy was also used with FOLFIRINOX. The response rate of FOLFIRINOX treatment was about 20–40%, similar to the ACCORD 11 trial [7]. However, the resection rate after FOLFIRINOX treatment varies among reports, maybe due to the different distribution of BR and UR cancer in each report. Moreover, there are no standard criteria for surgical resection. Most studies do not describe definite criteria for conversion surgery. For this reason, it is difficult to compare resection rates among studies. Even with these limitations, the conversion surgery following FOLFIRINOX treatment seems to be effective for the following reasons: first, the reported resection rate of locally advanced (UR) cancer varies among reports, from 6 to 44%, but R0 resection was achieved in most patients who underwent resection. Second, in most reports, the mortality rate was 0%, suggesting that FOLFIRINOX treatment did not affect the postoperative course. Third, a pathological complete response was seen in 5–15% of patients who underwent resection. Fourth, the prognosis of patients who

Table 1 Conversion surgery following FOLFIRINOX treatment for locally advanced pancreatic cancer

Author	Year	Ref.	*n*	Radiation	Resectability			Response rate	Resection rate	Resection rate for LAPC	R0 rate among resected cases	R0 rate for LAPC	90 days Mortality	pCR	Median OS	Median OS for SR patients
					R	BR	UR									
Chapman	2018	[48]	83	–	–	57 (68.7%)	26 (31.3%)	21 (25.3%)	55 (66.3%)	N.A.	52 (94.5%)	N.A.	2 (3.6%)	3 (5.5%)	23.5 m	27.4 m
Barenboim	2018	[47]	53	–	–	23 (43.4%)	30 (56.6%)	N.A.	23 (43.4%)	3 (10%)	23 (100%)	N.A.	0	3 (13%)	27.9 m (BR)	34.3 m (BR)
Marchegiani	2018	[46]	**59**[a]	1 (1.7%)	2 (3%)	11 (19%)	46 (78%)	N.A.	43 (72.9%)	N.A.	30 (69.8%)	N.A.	N.A.	N.A.	N.A.	N.A.
Michelakos	2017	[45]	**141**[a]	127 (90%)	–	72 (51.1%)	69 (48.9%)	N.A.	110 (78%)	N.A.	**87 (80.6%)**	N.A.	2 (1.4%) (30 days)	N.A.	34.2 m	37.7 m
Lakatos	2017	[44]	32		–	–	32 (100%)	6 (18.8%)	2 (6.3%)	2 (6.3%)	2 (100%)	2 (100%)	0 (0%)	N.A.	10.4 m	N.A.
Wagner	2017	[43]	**36**[a]	24 (67%)	2 (6%)	21 (58%)	13 (36%)	17 (47%)	–	–	31 (86%)	11 (85%)	N.A.	5 (14%)	–	N.A.
Khushman	2015	[42]	51	27 (53%)	–	11 (22%)	40 (78%)	N.A.	11 (22%)	N.A.	10 (91%)	N.A.	N.A.	1 (9%)	35.4 m	R0 resected: 67% at 3 years
Nitsche	2015	[41]	14	–	–	–	14 (100%)	6 (43%)	4 (29%)	4 (29%)	3 (75%)	3 (75%)	0 (0%)	0 (0%)	N.A.	31 m
Nanda	2015	[40]	29	29 (100%)	–	14 (48%)	15 (52%)	N.A.	12 (41.3%)	2 (13.3%)	10 (83.3%)	N.A.	0 (0%)	1 (8.3%)	18.6 m	50% at 1 year
Ferrone	2015	[35]	**40**[a]	30 (75%)	–	15 (37.5%)	25 (62.5%)	N.A.	–	–	35 (92%)	N.A.	0 (0%)	2 (5%)	–	34 m
Blazer	2015	[39]	43	23 (54%)	–	18 (42%)	25 (58%)	9 (23%)	22 (51.1%)	11 (44%)	19 (86%)	10 (91%)	0 (0%)	2 (9.1%)	21.2 m	Not reached
Boone	2013	[38]	21	12 (57%)	–	11 (52%)	10 (48%)	N.A.	11 (52%)	2 (20%)	7 (63.6%)	1 (50%)	0 (0%)	1 (9.1%)	N.A.	N.A.
Faris	2013	[37]	**22**[a]	20 (91%)	–	–	22 (100%)	6 (27.3%)	–	5 (22.7%)	5 (100%)	5 (100%)	N.A.	1 (20%)	N.A.	N.A.
Hosein	2012	[36]	18	0 (0%)	–	4 (22%)	14 (78%)	N.A.	9 (50%)	6 (43%)	8 (89%)	5 (83%)	N.A.	N.A.	Not reached	Not reached

Ref. reference, *n* total number of patients, *R* resectable, *BR* borderline resectable, *UR* unresectable, *Resection rate* rate of R0 or R1, *N.A.* not available, *LAPC* locally advanced pancreatic cancer, *pCR* pathological complete response, *OS* overall survival, *SR* surgically resected, *m* months

[a]Only surgically resected cases

underwent surgical resection was favorable, with more than 30 months median survival, although the observation periods were generally short and survival analyses were generally performed for BR and UR patients together, with only a few reports documenting the prognosis only for patients with UR cancer initially. Nevertheless, the favorable prognosis of patients given preoperative FOLFIRINOX treatment supports the benefits of conversion surgery following FOLFIRINOX treatment.

Preoperative CRT

CRT has also been given as preoperative treatment for pancreatic cancer. As described, CRT is expected to achieve better local tumor control than chemotherapy, which may lead to a better R0 resection rate. Many CRT regimens have been investigated, especially for BR cancer. Takahashi et al. reported their experience of using preoperative gemcitabine + radiation combination therapy, followed by surgical resection and liver perfusion chemotherapy to treat BR pancreatic cancer [49]. Even in patients with BR cancer and arterial involvement, the resection rate was 57% and the 5-year survival rate was 25% for patients who underwent resection.

Jang et al. from Korea reported the only prospective trial examining the effect of neoadjuvant CRT for BR cancer. They conducted a randomized phase II/III trial comparing neoadjuvant CRT with gemcitabine versus upfront surgery [50]. The R0 resection rate was higher (51.8% vs. 26.1%) and the median survival time was significantly longer (21 months vs. 12 months) in the neoadjuvant CRT group than in the upfront surgery group. These results indicate that CRT is also suitable as preoperative treatment for pancreatic cancer.

For metastasized pancreatic carcinoma

Pancreatic cancer metastasizes easily to other organs. At the time of diagnosis, two-thirds of pancreatic cancer patients already have metastasis [51]. For some other malignancies, such as colorectal cancer, synchronous resection of the primary tumor and metastases is thought to improve the prognosis; however, there are few reports of surgical resection of pancreatic cancer with synchronous metastases [52–55]. Nevertheless these reports included only selected patients, the prognoses after surgery were poor with about 10 months median overall survival [56]. Thus, the guidelines for the treatment of pancreatic ductal adenocarcinoma advocate systematic chemotherapy as the first-line treatment and do not recommend resection of the primary tumor and synchronous distant metastases without preoperative treatment [57, 58].

A few patients have shown remarkable response to the new chemotherapy regimen and, in some cases, the metastatic tumors become undetectable on imaging scans. Conversion surgery might be an option for these patients, but so far, there are limited reports, and mainly case reports, on conversion surgery for metastasized pancreatic cancer [59, 60]. Table 2 summarizes the representative reports on conversion surgery for metastasized pancreatic cancer.

Wright et al. [61] analyzed, retrospectively, 23 cases of surgical resection of Stage IV pancreatic cancer after a favorable response to systematic chemotherapy in two major institutes in the United States: Johns Hopkins Hospital and the University of Pittsburg. The sites of metastasis included the liver ($n=16$), lung ($n=6$), and peritoneum ($n=2$). They treated 1147 patients with Stage IV pancreatic cancer during the same period, and reported a resection rate of only 2.0%. They generally administered the FOLFIRINOX regimen and performed surgery a median 9.7 months after the diagnosis. The median overall survival times from the time of surgery and from the time of diagnosis were 18.2 months and 34.1 months, respectively. Although they reported favorable overall survival for selected patients, early recurrence was detected within 6 months of surgery in seven patients (30.4%). Moreover, they could not identify the best indicators for conversion surgery for metastasized pancreatic cancer: the CA19-9 level and radiologic responses during the chemotherapy were not associated with longer survival. This is the first report to analyze a number of cases of conversion surgery for metastasized pancreatic cancer; however, the criteria for conversion surgery were not clear.

Frigerio et al. [62] also analyzed cases of conversion surgery for pancreatic cancer with liver metastasis in two Italian high volume centers: the Pederzoli Hospital in Peschiera del Garda and the Pancreas Institute in Verona. The criteria for conversion surgery included the disappearance of liver metastasis and normalization or a marked decrease in the serum CA19-9 level. Again, FOLFIRINOX was given mainly as the preoperative chemotherapy. Twenty-four (4.5%) of their 535 patients with pancreatic cancer and liver metastasis met the above criteria and underwent surgical resection of the primary site and hepatic resection if the metastatic site was still evident. The median duration from diagnosis to surgical resection was 10 months, similar to that of Wright's report. R0 resection was performed in 21 patients (88%), 4 of whom showed a pathological complete response. The median overall survival time from diagnosis was, surprisingly, 56 months, and the median disease-free time from surgery was 27 months.

Satoi et al. [63] also reported the effectiveness of conversion surgery for pancreatic cancer with peritoneal metastasis in their phase II study examining the effectiveness of intravenous and intraperitoneal paclitaxel treatment vs. systemic S-1 treatment. Eight of the 33 patients enrolled in the study underwent conversion surgery and the overall survival of these patients was significantly longer than

Table 2 Conversion surgery for metastasized pancreatic cancer

Author	Year	Ref.	*n*	Metastatic site, number	Treatment regimen	Resection rate	Time from diagnosis to surgery	Median DFS from surgery	Median OS from diagnosis	Median OS from surgery
Frigerio	2017	[62]	24	Liver: 24	FOLFIRINOX, GnP, GEM	24/535 (4.5%)	Median: 10 m	13 m	56 m	N.A.
Wright	2016	[61]	23	Liver: 16, lung: 6, peritoneum: 2	FOLFIRINOX, GEM based	N.A.	Median: 9.7 m	8.6 m	34.1 m	18.2 m
Satoi	2016	[63]	8	Peritoneum: 8	PTX ip + PTX iv, S-1 po	8/33 (24%)	> 8 m in all cases	N.A.	27.8 m	N.A.

Ref. reference, *n* patients' number, *GnP* gemcitabine + albumin bound paclitaxel, *GEM* gemcitabine, *ip* intraperitoneal, *iv* intravenous, *po* per os, *N.A.* not available, *m* months, *DFS* disease-free survival, *OS* overall survival

that of the non-surgically treated patients (27.8 months vs. 14.2 months, respectively; $P = 0.0038$).

In all reports, the numbers of patients who underwent conversion surgery following systemic therapy were limited, accounting for less than 5% of those with metastasized pancreatic cancer and there were very few long-term survivors. Based on these limited data, the usefulness of conversion surgery for metastasized pancreatic cancer remains controversial, although one potential benefit is that it may give the patient an extended time off chemotherapy and potentially maintain their quality of life. In these reports, a small number of patients survived for more than 5 years (10–20%). To select which patients are most likely to benefit from conversion surgery, it is essential to identify the predictive markers for long-term survival after conversion surgery.

Unresolved questions about conversion surgery

Despite the evidence that conversion surgery can improve the survival of patients with initially unresectable pancreatic cancer, many questions remain unresolved.

What is the optimal preoperative therapy?

A wide variety of treatment regimens are used as preoperative therapy and there is no standard treatment protocol. In addition to FOLFIRINOX, GnP is also thought to be efficient as preoperative therapy, but there are very few reports on conversion surgery after giving GnP as preoperative therapy. Ilepo et al. first reported the safety and efficacy of GnP as preoperative treatment in their analysis of patients who were given GnP prospectively for resectable or BR pancreatic cancer [64, 65]. They reported that the median survival of patients who underwent resection after preoperative treatment was significantly longer than that of patients who underwent resection without preoperative treatment for patients with BR. However, for patients with resectable cancer, there was no statistical difference in survival between those who received vs. those who did not receive preoperative GnP treatment. This result suggests that preoperative GnP treatment may improve the survival of patients with relatively advanced cancer. Recent reports comparing FOLFIRINOX and GnP showed that both treatments are a viable option for preoperative treatment, although FOLFIRINOX was associated with slightly better survival in the adjustment analysis [48, 66]. As those studies were retrospective and the patients' characteristics differed between those treated with FOLFIRINOX and those treated with GnP, it is hard to conclude which is the best for preoperative therapy. We are waiting for the results of a randomized control study comparing both treatments.

Preoperative radiation therapy combined with chemotherapy also remains controversial. More than half of the patients in a recent systemic review of FOLFIRINOX-based preoperative treatment given for locally advanced pancreatic cancer also received radiation therapy [67]. A lower resection rate was seen in patients who received only FOLFIRINOX treatment than in patients who also received radiation therapy (12% vs. 28%). Pathological complete response was seen in 7% of all the patients, but in none of those who received FOLFIRINOX treatment only. These data may indicate the usefulness of radiation therapy combined with systemic chemotherapy, although the survival benefit of radiation therapy remains unclear because of the short observation period in most of the analyzed studies.

On the other hand, Kim et al.[68] reported that combination with radiation therapy did not improve the survival of patients treated with preoperative FOLFIRINOX for their BR pancreatic cancer. A study investigating recurrence patterns after margin-positive surgical resection found distant metastasis first in 55.1% of patients [69]. Similarly, an autopsy analysis of patients who had been treated with surgical resection revealed that 70–85% died of systemic recurrence rather than local recurrence [70], emphasizing the importance of systemic chemotherapy over radiation therapy as preoperative treatment for pancreatic cancer. Future prospective studies comparing preoperative therapy with or without radiation are necessary.

Optimal duration of preoperative therapy

The optimal duration of preoperative therapy is also under debate. As described in following section, there is no indicator for surgical resection after preoperative therapy. In their multicenter survey of Japanese institutions, Satoi et al. [13] found a significantly favorable difference in the overall survival of patients who underwent conversion (or adjuvant) surgery more than 240 days after their initial treatment. Most of the patients in this analysis were treated with gemcitabine-based C(R)T. The median duration between the initial therapy and the detection of partial response (PR)/complete response (CR) was 150 days and the median duration between the detection of PR/CR and surgical resection was 127 days. According to this report, several institutions, especially in Japan, tended to treat patients with C(R)T for a relatively long time before resection [71, 72].

On the other hand, Gemenetzis et al. from Johns Hopkins University [73] reported the favorable overall survival of 84 patients with locally advanced cancer surgically resected after preoperative therapy (median survival time: 35.3 months) in their retrospective analysis. The median duration of neoadjuvant therapy in these patients was 5 months. The decision to offer surgical exploration was made after ≥ 4 months of chemotherapy and/or in the absence of disease progression, being shorter than that reported by Satoi et al. [13].

FOLFIRINOX and GnP are given mainly for unresectable pancreatic cancer, recently. One of the problems of these new regimens is the high incidence of adverse events [7, 8]. In phase III trials for metastatic pancreatic cancer, the ratio of grade 3 or 4 neutropenia was high, at about 40–45%. Moreover, sensory neuropathy of grade 3 or higher, which compromises quality of life severely, was seen in 9% of patients given FOLFIRINOX and 17% of those given GnP. Moreover, oxaliplatin and irinotecan, which are components of FOLFIRINOX, are both known to cause liver damage [74]. With these high rates of adverse events, it might be difficult to treat patients with these new chemotherapy regimens for a long time. It should be also noted that these new regimens took less time to achieve a RECIST response (median time to response was 40–50 days), in phase II trials in Japan [20, 21]. These results may indicate that using these new chemotherapy regimens, a long duration of preoperative therapy is not necessary for conversion surgery. In fact, Michelakos et al. reported that > 8 months between diagnosis and surgery predicted a shorter postoperative disease-free survival in their analysis of 110 patients with BR or UR pancreatic cancer who underwent resection after FOLFIRINOX preoperative therapy [45].

Management of obstructive jaundice is also a problem associated with long-term preoperative therapy. Although biliary drainage is required to reduce the bilirubin level in patients with obstructive jaundice to treat them with chemotherapy, stent obstruction leads to cholangitis and can interrupt C(R)T. The median time to stent obstruction using a plastic stent is reported to be only 2–5 months [75]. A recent meta-analysis showed a lower re-intervention rate for a covered expandable metallic stent (EMS) vs. a plastic stent for preoperative treatment [76]. However, the rate of overall complications related to preoperative biliary drainage was reported to be about 30%. Preoperative cholangitis may also increase the incidence of postoperative complication [77]. These results indicate that prolonged preoperative treatment may be problematic for patients with obstructive jaundice.

Conversion surgery for metastatic cancer tends to be performed after a long duration (about 10 months) of preoperative therapy and only if obvious effects are seen [61, 62]. The optimal duration of preoperative therapy is still not clear and should be decided by considering treatment regimens, adverse events, response to preoperative therapy, and performance status in each patient.

Portal and arterial resection

Tumor infiltration to the vasculature surrounding the pancreas is the main reason for unresectability of locally advanced pancreatic cancer. Therefore, concomitant vascular

resection and reconstruction are often required in conversion surgery for curative resection.

Portal vein (PV) and/or supra-mesenteric vein (SMV) resection is generally performed for pancreatic cancer resection with infiltration to the PV/SMV to achieve curative resection and is recommended in the clinical guidelines [22, 23]. However, in conversion surgery, the portal vein is often infiltrated widely and an interposed venous conduit is usually required for reconstruction. An internal jugular, external iliac or saphenous vein graft is used for this purpose [78]. We reported the usefulness of a left renal vein graft for portal vein reconstruction [79–81]. This graft has several advantages over other grafts because it can be procured quickly without the need for an additional skin incision during surgery and its diameter usually matches the PV/SMV. Moreover, reconstruction of the renal vein is not necessary because of the existence of collateral veins such as the gonadal vein. Considering these advantages, the left renal vein graft is now used worldwide [82–84].

On the other hand, arterial resection for pancreatic cancer remains controversial and is associated with significantly high morbidity and mortality rates [85, 86]. Mollberg et al. [87] conducted a systematic review and meta-analysis of 26 studies, including 366 patients who underwent arterial resection concomitant with pancreatectomy for pancreatic cancer. They reported that arterial resection was associated with a significantly higher risk of perioperative mortality, five times that of patients without arterial resection. Moreover, survival at 1 year and 3 years was worse for patients who underwent arterial resection than for those who did not. In their systematic review of 13 studies on SMA resection during pancreatectomy for malignant disease of the pancreas, Jegatheeswaran et al. [88] also reported a relatively high mortality rate (5 of 25) among patients who underwent SMA resection, whose median survival was only 11 months. According to these data, arterial infiltration has been considered as contraindication to surgical resection for pancreatic cancer.

Some recent studies have shown the efficacy of arterial resection for selected patients. Hirano et al. [89] reported the efficacy and safety of distal pancreatectomy with en bloc celiac axis resection (DP-CAR) for pancreatic body cancer invading the CEA, and this procedure has been widely accepted. A recent systematic review of 240 patients who underwent DP-CAR showed acceptable safety, with a 3.5% 90-day mortality rate and overall median survival of 14.4 months [90]. Although this systematic review showed a limited survival benefit of DP-CAR, there is now some evidence of the improved survival of patients who have undergone DP-CAR when combined with perioperative CRT [91, 92].

Recent reports on CHA or SMA resection also document a low mortality rate (0–9%) [93–97]. Bachellier et al. from the Universitaires de Strasboug (France) [98] reported the largest series of arterial resection for pancreatic cancer in a single institute. They analyzed 118 consecutive patients who underwent arterial resection concomitant with pancreatic resection between 1990 and 2017, including 35 with SMA, 51 with CEA, and 29 with CHA. The overall mortality rate of 5.1% was acceptable and the median overall survival was 13.7 months. Although the survival data were not satisfactory, 10 patients had survived for more than 3 years after surgery. After preoperative chemotherapy, the median overall survival calculated from the initiation of neoadjuvant treatment was 22.85 months. Interestingly, few patients survived more than 3 years even in the presence of stage IV disease.

According to these data, arterial resection concomitant with pancreatectomy to achieve curative resection might benefit selected patients. However, there are no established indicators for selecting patients who will benefit from arterial resection. Considering the high morbidity and mortality rates of this procedure, arterial resection should be performed only in highly experienced centers under the careful scrutiny of a multidisciplinary treatment team.

Predictive factors of resection and survival

Many studies have tried to identify the predictive factors of survival after conversion surgery, to establish better indicators for patient selection. However, no such factors have been identified. Imaging response to preoperative treatment is not adequate to determine resectability and survival. According to recent studies, most patients who underwent conversion surgery had no evidence of a response on imaging and there was no survival difference between responders and non-responders [35, 43, 67, 73, 99, 100]. Moreover, in several studies, the accuracy of CT in determining resectability was significantly decreased after preoperative treatments [43, 99]. According to these results, imaging response cannot be used to select patients for conversion surgery.

Measuring the CA19-9 level may be a useful predictor of survival. Normalization or a marked decrease in the CA19-9 level following preoperative treatment was reported to correlate with better survival [45, 100, 101]; however, there is no consensus criteria for the CA19-9 level on which to base the selection of patients who could benefit from conversion surgery.

Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET)/ computed tomography (CT) may be useful for predicting postoperative survival. Akita et al. [102] reported that the regression index of positive standard uptake values (SUV), being the ratio of SUV before and after preoperative treatment, was an independent prognostic factor for patients with resectable and BR pancreatic cancer. A recent meta-analysis also showed that a reduction in SUV during preoperative treatment correlated with resectability

in patients with BR and UR pancreatic cancer [103]. On the other hand, there are several problems associated with PET/CT, which can be affected by the status of diabetes mellitus, a common comorbidity of pancreatic cancer. Moreover, SUV shows inter- and intra-scanner variability and harmonization is the key to the standardization of this examination.

Many investigators have reported that a complete pathological response by preoperative treatment correlated with better survival [72, 104]. He et al. [105] conducted a retrospective analysis of 186 patients with BR or locally advanced UR pancreatic adenocarcinoma, who underwent neoadjuvant chemoradiation and subsequent pancreatectomy. In their analysis, pathological complete response (pCR) was achieved in 19 patients (10%) and nearly pathological complete response (nCR) was achieved in 29. Surprisingly, the median overall survival of patients with a pCR was 60 months, which was significantly longer than that of the nCR patients. However, identifying the pathological effects preoperatively is difficult. Endoscopic ultrasound-fine needle aspiration (EUS-FNA) biopsy is often used for pathological analysis before surgery, but the small tissue sample taken is usually insufficient to determine the pathological effects.

Prospective studies

Many questions about conversion surgery remain unresolved and several prospective studies are in progress. Table 3 summarizes the ongoing prospective studies for locally advanced pancreatic cancer, including surgical resection as primary or secondary endpoint. A wide variety of treatment regimens are being examined. The NEOPAN study (NCT02539537), the only phase III study among them, was designed to evaluate the efficacy of FOLFIRINOX versus gemcitabine for

Table 3 Ongoing clinical trials of conversion surgery for locally advanced pancreatic cancer

Registration number	Study name	Objective	Interventions (preoperative therapy)	Phase	Country	Study started
NCT02539537	NEOPAN	UR	Arm1) Gemcitabine Arm2) FOLFIRINOX	III	France	2015
NCT03652428		UR	GnP → Radiation (HAPT)	I, II	US	2018
NCT03599362		UR	Nivolumab + Cabiralizumab → SBRT	II	US	2018
NCT03523312	MAIBE	UR	Capecitabine + HFA-IMRT	II	US	2018
UMIN000030551		UR	GnP + Radiation	I	JP	2018
NCT03641183		BR/UR	Arm1) GnP → SBRT Arm2) FOLFIRINOX → SBRT	I, II	US	2017
NCT03316326		UR	SIROX (S-1, Irinotecan, Oxaliplatin)	II	Taiwan	2017
UMIN000028116	NUPAT 05	UR	GnP + Radiation	II	JP	2017
UMIN000023217		UR	GnP → Radiation + S-1	II	JP	2016
UMIN000022241	CAP-005	BR/UR	GnP	II	JP	2016
UMIN000017793	Prep-04	UR	Not determined	Observational	JP	2015
UMIN000017694	PK-NACRT-Gmet	BR/UR	Metformin + Gemcitabine + Radiation	II?	JP	2015
UMIN000016630	GAS Study	UR	Gemcitabine + nab-PTX + S-1	I, II	JP	2015
NCT02210559		UR	Arm1) FG-3019 + GnP Arm2) GnP	I, II	US	2014
UMIN000015707		BR/UR	modified FOLFIRINOX	II	JP	2014
UMIN000014039		UR	FOLFIRINOX	II	JP	2014
UMIN000013385		UR	FOLFIRINOX	II	JP	2014
NCT01959672		BR/UR	Gemcitabine + Leucovorin ± Oregovomab → SBRT → nelfinavir	II	US	2013
NCT01821729		UR	FOLFIRINOX + Losartan → Proton beam ratiation	II	US	2013
UMIN000011453		BR/UR	Gemcitabine + S-1 + Radiation	II	JP	2013
UMIN000012250		UR	Arterial infusion chemotherapy + chemoradiation	II	JP	2013
NCT01760252		R/BR/UR	CAPOXIRI	II	US	2011
NCT01360593		BR/UR	Gemcitabine + Capecitabine → SBRT	II	US	2011

Studies including surgical resection for locally advanced pancreatic cancer as the primary or secondary endpoint as listed in Clinicaltraials.com or UMIN

R resectable pancreatic cancer, *BR* borderline resectable pancreatic cancer, *UR* unresectable pancreatic cancer, *GnP* Gemcitabine + albumin bound Paclitaxel, *FOLFIRINOX* 5-fluorouracil + Folic acid + Oxaliplatin + Irinotecan, *FG-3019* Pamrevlumab, *CAPOXIRI* Capecitabine + Oxaliplatin + Irinotecan, *nab-PTX* albumin bound Paclitaxel, *HAPT* hypofractionated ablative pancreatic proton radiation therapy, *SBRT* stereotactic body radiotherapy, *HFA-IMRT* hypofractionated ablative IMRT, *IMRT* intensity-modulated radiation therapy

unresectable locally advanced pancreatic cancer. The percentage of secondarily curative-intent operations is one of the secondary outcomes of this study.

One of the problems of prospective trials is that the definition of unresectability differs among trials, many of which include borderline resectable cancer cases. On the other hand, cases of extreme cancer spread, such as invasion of the aorta or adjacent organs, are usually excluded. Moreover, there are no standard criteria for surgical resection after preoperative therapy. To establish "unresectability" will be the key for future meta-analyses of these prospective studies.

Conclusion

There is growing evidence of the efficacy and safety of conversion surgery for locally advanced and also metastasized pancreatic cancer. However, many questions remain unresolved about the optimal treatment regimen, duration of preoperative treatment, and criteria for surgical resection. The results of prospective studies will gradually answer these questions. It should be emphasized that conversion surgery is performed only in experienced high-volume centers as it requires specialized decision-making and patient care.

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Compliance with ethical standards

Conflict of interest Hideyuki Yoshitomi and his co-authors have no conflicts of interest to declare.

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