Treatment for postoperative recurrence of pancreatic cancer: a narrative review

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Background and Objective: Patients with pancreatic cancer frequently develop postoperative disease recurrence, even after surgical resection with curative intent. Because of the heterogeneity of this patient population, phase III trials have never been conducted to establish a standard therapy for patients with post-surgical recurrence, and no uniform consensus based on high-level evidence exists as to which intervention might be the most appropriate. The aim of this review is to introduce globally popular treatment strategies for pancreatic cancer patients with postoperative recurrences.

Methods: This is a narrative review, summarising the contemporary evidence and emerging studies with treatment for postoperative recurrence of pancreatic cancer.

Key and Content and Findings: For patients with local recurrence alone, various therapeutic strategies have been attempted, including repeat surgical resection, chemoradiotherapy, and chemotherapy alone. Several studies have examined the outcomes of these therapies, but most are retrospective analyses of a small number of patients and statistically too underpowered to allow any solid recommendations to be made. Therefore, with the exception that there appears to be a potential benefit of repeat resection for isolated recurrences in the pancreatic remnant in a selected subgroup of patients, the patient outcomes remain dismal. In regard to the management of patients with distant recurrences, postoperative distant recurrences are generally not considered as being distinct from primary metastatic disease, and most patients with distant recurrence(s) with/without local tumor recurrence receive systemic chemotherapy as the standard therapy for metastatic disease; some studies have demonstrated a trend toward better survival outcomes in patients with a history of surgical resection than in those without a history of surgical resection.

Conclusions: Although no uniform consensus based on high-level evidence exists, systemic chemotherapy has been used as the main treatment option, and some regimens have been demonstrated to offer a survival benefit. There is an urgent need for prospective trials to establish the most appropriate treatment strategies for this patients' population.

Keywords: Pancreatic resection; recurrence; re-resection; chemoradiotherapy; chemotherapy

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Introduction

Pancreatic cancer remains one of the most challenging malignancies to treat. Of all the modalities available for the treatment of pancreatic cancer, only resection offers an opportunity for cure. However, even among patients with resectable disease, the long-term outcomes remain unsatisfactory, with 5-year survival rates remaining a dismal 10–40%, because most patients develop recurrence even after resection with curative intent (1-10). It is speculated that the major reasons for these poor outcomes are the presence of occult systemic tumor spread (which are responsible for distant metastasis) even at the time of diagnosis, and the microscopic persistence of malignant cells around the resection area (which are responsible for

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	01 June 2021
Databases and other sources searched	Medline, PubMed, NCCN Clinical Practice Guidelines in Oncology, ESMO Clinical Practice Guidelines
Search terms used (including MeSH and free text search terms and filters)	Pancreatic cancer, pancreatic resection, recurrence, treatment, re-resection, chemoradiotherapy, chemotherapy
Timeframe	Between July 1990 and September 2021
Inclusion and exclusion criteria (study type, language restrictions, etc.)	Included in the review were retrospective or prospective clinical studies published in English
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	The author conducted the selection
Any additional considerations, if applicable	Additional data have been included under the revision

NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology.

local recurrence) after a macroscopically curative tumor resection.

This review focuses on the management of local and distant recurrences developing after surgical resection in patients with pancreatic cancer. No phase III trials have ever been conducted in this patient population, and literature on this topic remains limited. While it has therefore been difficult to establish standard management strategies for this category of patients, globally popular treatment strategies for pancreatic cancer patients with postoperative recurrences and future perspectives in this field are introduced in this article. I present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-87/rc).

Methods

Medline, PubMed, and various international evidence-based guidelines [like National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology] were searched for the current status of treatment for postoperative recurrence of pancreatic cancer (*Table 1*). Included in the review were English, retrospective or prospective clinical studies published between July 1990 and September 2021.

Discussion

Rates and sites of recurrence after pancreatic resection

Most pancreatic cancer patients develop recurrence after surgery, even after surgical resection with curative intent. According to most recent clinical trials and retrospective series, the median time to recurrence is between 5 and 23 months in (3-16). This period has been gradually extended with the introduction of adjuvant chemotherapies or chemoradiotherapies established on the basis of well-designed, randomized, controlled trials, although their impact still remains limited (3-10) (*Table 2*). Several randomized studies have demonstrated that extended lymphadenectomy had no impact on either the recurrence rate or the pattern of recurrence (17-19).

Locoregional recurrence is the major pattern of recurrence after pancreatic cancer resection: 8–53% of cases present with only local recurrence as the initial recurrence, without evidence of distant recurrence. The incidence of postoperative local recurrence has apparently remained fairly unchanged even after the introduction of adjuvant local therapies such as postoperative chemoradiotherapy, although available data are limited (3,6). The time to diagnosis of local recurrence in this population is almost the same as the time to diagnosis of distant recurrence; according to several reports, the median interval from

Table 2 Rates and patterns of recurrence in recent randomized trials of adjuvant therapy after pancreatic cancer resection

Treatment (modality)	Author, year (ref)	Study name	Regimen	Follow-up period (months), median [range]	Recurrence rate, % (n/N)	Recurrence pattern (%)			DFS (months), median
						L	L + D	D	
Surgery alone	Klinkenbijl JH, 1999 (3)	EORTC	Surgery alone	NA	66 (68/103)	22	32	43	16.0
	Oettle H, 2007 (4)	CONKO-001	Surgery alone	53 [9–96]	92 (161/175)	41		49	6.9
	Ueno H, 2009 (5)	JSAP 02	Surgery alone	60.4 [40.6–77.1]	88 (53/60)	32	NA	66	5.0
Surgery + adjuvant CRT	Klinkenbijl JH, 1999 (3)	EORTC	CRT	NA	65 (67/104)	22	28	48	17.4
	Regine WF, 2011 (6)	RTOG 9704	CRT + 5-FU	1.48 [0.1–9.1] years	89 (205/230)	30	NA	70	NA
			CRT + gemcitabine		88 (195/221)	25	NA	78	NA
–	Neoptolemos JP, 2004 (7)	ESPAC-1	All groups*	42 [33–62]	55 (158/289)	35	27	34	NA
Surgery + adjuvant chemotherapy	Oettle H, 2007 (4)	CONKO-001	Gemcitabine	53 [9–96]	74 (133/179)	34		56	13.4
	Ueno H, 2009 (5)	JSAP 02	Gemcitabine	60.4 [40.6–77.1]	76 (544/58)	23	NA	75	11.4
	Neoptolemos JP, 2004 (7)	ESPAC-3	5-FU + FA	34.2 [27.1–43.4]	63 (688/1,088)	NA			15.1
			Gemcitabine						14.3
	Uesaka K, 2016 (8)	JASPAC01	S-1	79.3 [72.0–89.0]**	66 (123/187)	19	NA	NA	22.9
			Gemcitabine	82.3 [71.8–88.5]**	78 (149/190)	26	NA	NA	11.3
	Neoptolemos JP, 2017 (9)	ESPAC-4	Gemcitabine + capecitabine	43.2 [39.7–45.5]***	65 (236/364)	46	NA	NA	13.9
			Gemcitabine		66 (243/366)	53	NA	NA	13.1
	Conroy T, 2018 (10)	PRODIGE 24-ACCORD 24/CCTG PA 6	Modified FOLFIRINOX	33.6 [30.3–36.0]***	54.2 (134/247)	25	18	52	21.6
			Gemcitabine		73.2 (180/246)	24	23	46	12.8

*, all groups include the CRT group, 5-FU + leucovorin group, CRT + 5-FU + leucovorin group, and surgery-alone group in the ESPAC-1 trial; **, interquartile range; ***, 95% CI. CRT, chemoradiotherapy; 5-FU, 5-fluorouracil; FA, folinic acid; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; NA, not available; L, locoregional; L + D, locoregional plus distant recurrence; D, distant recurrence; DFS, disease-free survival; CI, confidence interval.

resection until recurrence is around 9–11 months, for both local recurrence and distant recurrence (11-16) (*Table 3*).

On the other hand, distant recurrence is another major pattern of recurrence after pancreatic surgery; 14–78% of patients present with only extra-pancreatic recurrence as the initial recurrence, while 18–78% patients present with combined locoregional and distant recurrence. The most common sites of distant recurrence are the liver, lymph node, and peritoneum, followed in frequency by the lung, bone, and other distant sites, including the brain (14-16,20). Distant recurrence is serious, not only because it is the major pattern of recurrence, but also because it indicates systemic tumor spread. The median survival period after diagnosis of a distant recurrence is 3.0–19.0 months, although a more favorable outcome has been reported in patients with isolated pulmonary metastases (12,13,15,16).

Management of local recurrence

Among patients diagnosed as having recurrence after resection for pancreatic cancer, 8–53% exhibit local recurrence without distant metastases (3,5-16). Various therapeutic strategies have been attempted, although no uniform consensus based on high-level evidence exists as to

Table 3 Recurrence patterns and survival periods in retrospective studies

Author, year (ref)	Number of patients with recurrences	Pattern of initial recurrence (%)			Time to recurrence (months), median			Survival after recurrence (months), median		
		L	L + D	D	L	L + D	D	L	L + D	D
Griffin JF, 1990 (11)	26	27	43	30	NA	NA	NA	NA	NA	NA
Westerdahl J, 1993 (12)	74	8	78	14	15	6	4	23	9	7
Sperti C, 1997 (13)	78	33	40	27	9.5	6.0[a]	9.0[b]	7.0	3.0[c]	
Van den Broeck A, 2009 (14)	110	17	23	60	NA	NA	NA	NA	NA	NA
Zhang Y, 2012 (15)	72	31	24	46	9.3	7	7.5	10.4	5.5	5.8
Kolbeinsson H, 2021 (16)	221	17	67	16	11.0[d]	NA	5.0–11.0[e]	3.0[d]	NA	4.0–19.0[e]

[a], locoregional and hepatic recurrence; [b], hepatic recurrence; [c], hepatic recurrence or locoregional and hepatic recurrence; [d], local and peritoneal recurrence; [e], liver and lung recurrence. L, locoregional; L + D, locoregional plus distant recurrence; D, distant recurrence; NA, not available.

which intervention might be the most appropriate for this subset of patients.

Surgery for local recurrence

Repeat surgical resection is one of the therapeutic options for patients with pancreatic adenocarcinoma presenting with an isolated recurrence, including local recurrence (21-34) (*Table 4*). A local recurrence is usually defined as a recurrent lesion localized to the resection bed, the pancreatic remnant, or the mesenteric root: the site of recurrence is usually diagnosed by preoperative imaging, intraoperative gross examination, and postoperative histopathological findings in case of operable recurrence, although a definitive diagnosis is sometimes difficult. Repeat surgical resection may be beneficial for a selected subgroup of patients with isolated local recurrence, for example, patients with a good performance status, with recurrence localized only in the remnant pancreas, with no major vessel invasion, and with no active neural invasion, because complete resection with a negative surgical margin at the second resection is relatively more likely to be achieved in such cases. The median survival time after repeat surgical resection appears to be relatively more favorable (25–44 months) in patients with recurrence localized to the pancreatic remnant (25,27,30,31).

Serafini *et al.* performed a systematic review/meta-analysis to determine the outcomes of repeat surgical resection in pancreatic cancer patients with isolated postoperative local recurrence (35). Six studies involving 431 patients with recurrent pancreatic cancer were included in the analysis, including 176 who had undergone repeat surgery and 255 who had undergone non-surgical treatments. After surgery for local recurrence, the reported mortality rate was 1.1% (2/176 patients) (24,33); the morbidity rate ranged from 6% (33) to 33% (31). The overall survival and post-recurrence survival were significantly longer in the repeat resection group, with a median overall survival period of 28.7 months. They concluded that resection for isolated pancreatic cancer recurrence is safe and feasible and may offer survival benefit. Miyasaka *et al.* reviewed the developmental mechanisms, predictive factors, and treatments of high-risk lesions (HRLs), including high-grade pancreatic intraepithelial neoplasia (PanIN), pancreatic ductal adenocarcinoma, high-grade intraductal papillary mucinous neoplasm (IPMN), and IPMN with associated invasive carcinoma in the remnant pancreas after partial pancreatic resection for pancreatic cancer or IPMN (36). They suggested that HRLs in the remnant pancreas may occur even long after the initial operation, and that life-long surveillance may be necessary in patients undergoing partial pancreatic resection for pancreatic cancer or IPMN.

The most common surgical procedure employed for local recurrence in the remnant pancreas is total remnant pancreatectomy, although partial pancreatectomy is performed some cases (25,37). Laparoscopic and robotic resection for postoperative pancreatic cancer recurrence are still uncommon as alternative approaches to open surgery, although several surgeons have reported favorable results of these surgical procedures for postoperative local recurrence

Table 4 Surgical treatment for recurrence of pancreatic cancer

Author, year (ref)	N	Type of recurrence		Median overall survival (months)	Median survival after recurrence (months)
		Local	Distant		
Kleeff J, 2007 (21)	15	15	0	17	NA
Strobel O, 2013 (24)	41	41	0	NR	26
Miyazaki M, 2014 (25)	11	11	0	78.2	25
Shima Y, 2015 (27)	6	6	0	49	27.5
Chang SC, 2016 (28)	14	14	0	57.8	14.1
Nakayama Y, 2018 (30)	11	11	0	70	44
Yamada S, 2018 (31)	90	90	0	NR	26
Arnaoutakis GJ, 2011 (22)	9	0	9**	51	18.6
Yasukawa M, 2017 (29)	12	0	12**	121	47
Groot VP, 2019 (32)	19	0	19**	68.9	35
Thomas RM, 2012 (23)	21	7	14***	81.1	36
Boone BA, 2014 (26)	22*	10	12****	60.6	28.1
Kim YI, 2019 (33)	48	15	33*****	40.4	23.6

*, 6 patients with ampullary cancer were included; **, all patients had isolated pulmonary recurrence; ***, 7 patients had lung, 9 had liver, 1 had brain, and 1 had abdominal-wall metastasis; ****, 5 patients had lung, 6 had liver, and 1 had ovarian metastasis; *****, 15 patients had lung, 13 had liver, and 5 had other-organ metastasis. NR, not reported.

of pancreatic cancer (38-41).

Chemotherapy and/or radiotherapy for local recurrence

While surgical resection offers the only opportunity for cure, it is extremely difficult to achieve complete resection of the disease by repeat resection in patients with local recurrence of pancreatic cancer, and the prognosis of most patients undergoing repeat resection remains dismal. Therefore, repeat surgical resection, with its low success rate, may be too invasive for patients expected to have a poor prognosis, and should be exclusively proposed to patients who are eligible for potential R0 resection. Effective non-surgical treatments are needed as alternatives to repeat resection in patients who are not suitable candidates for repeat resection, or as induction therapies before repeat resection: chemoradiotherapy could be useful as combined local plus systemic therapy with the potential to surpass the benefit of resection in terms of the lower degree of invasiveness and satisfactory tumor control potential.

Data on chemoradiotherapy for postoperative local recurrences of pancreatic cancer after surgical resection are limited (42,43). However, recently, some prospective studies have either been planned or conducted to assess the efficacy/safety of combined chemoradiotherapy. A randomized controlled trial is being planned to evaluate the usefulness of stereotactic body radiotherapy (SBRT) in addition to the standard of care in patients with postoperative local recurrence as compared to the standard of care alone, with regard to both survival and quality of life outcomes (NCT04881487). Another randomized controlled phase II trial conducted to evaluate the usefulness of SBRT plus pembrolizumab and trametinib as compared to SBRT plus gemcitabine in locally recurrent pancreatic cancer patients with mutant *KRAS* and positive tumor immunohistochemical staining for PD-L1 (44) reported a median overall survival of 24.9 months in the SBRT plus pembrolizumab and trametinib arm, and 22.4 months in the SBRT plus gemcitabine arm (hazard ratio: 0.60; P=0.0012). The authors concluded that the results of this study need to be validated by a phase III study.

Groot *et al.* conducted a systematic review of treatments employed for isolated local recurrence after pancreatic resection (45), including repeat surgical resection (8 studies, 100 patients), chemoradiotherapy (7 studies, 153 patients), and stereotactic body radiation therapy (SBRT) (4 studies,

60 patients). The reported morbidity and mortality rates were 29% and 1% for repeat surgical resection, 54% and 0% for chemoradiotherapy, and 3% and 1% for SBRT, respectively. The reported median survival periods after treatment of isolated local recurrence were 32 months for re-resection, 19 months for chemoradiotherapy, and 16 months for SBRT. They suggested that the above treatments for isolated postoperative local recurrence of pancreatic cancer seem to be safe and feasible and to be associated with relatively good survivals in selected patients.

Management of distant recurrences

Chemotherapy for distant recurrences

In regard to the management of patients with distant metastases, recurrent disease is, in general, not considered as being distinct from primary metastatic disease, and most patients with distant recurrence, with or without local tumor recurrence, receive systemic chemotherapy as the standard therapy for metastatic disease. Most current guidelines recommend FOLFIRINOX therapy or combined gemcitabine plus nab-paclitaxel therapy as the first-line treatment for pancreatic cancer patients with distant metastases and a good performance status, olaparib for those with germline *BRCA* mutations, pembrolizumab for those with microsatellite instability (MSI)-high, entrectinib or larotrectinib for those with *NTRK* gene mutations, and combined nanoliposomal irinotecan plus 5-fluorouracil (5-FU) and leucovorin therapy as maintenance or second-line treatment. However, no global consensus exists in regard to the most suitable chemotherapy regimens for postoperative disease recurrence in patients who have already received postoperative adjuvant chemotherapy. For patients in whom the interval from completion of postoperative adjuvant therapy to detection of postoperative recurrence is less than 6 months, the NCCN guidelines recommend administration of an alternative chemotherapy regimen (46); on the other hand, for patients in whom this interval is 6 months or longer, they recommend an alternative regimen or the same regimen as that used for the postoperative adjuvant therapy.

We retrospectively reviewed the clinical data of 41 patients with distant recurrence who had received postoperative adjuvant chemotherapy (47). We divided the patients into two groups according to the interval from completion of adjuvant chemotherapy with gemcitabine to diagnosis of recurrence (<6 *vs.* ≥6 months, as per the recommendation in the NCCN guidelines): ADJ-Rec <6 months (n=25) and ADJ-Rec ≥6 months (n=16). The disease control rate, progression-free survival period after completion of treatment for recurrence, and the overall survival after recurrence in the two groups were 68% and 94% (P=0.066), 5.5 and 8.2 months (P=0.186), and 13.7 and 19.8 months (P=0.009), respectively. Then, we further subdivided the patient group with ADJ-Rec <6 months into two groups: a group in which the recurrent disease was treated with gemcitabine for (n=6) and a group in which the recurrent disease was treated with alternative regimens, including fluoropyrimidine-containing regimens (n=19). In our analysis, the results revealed that the outcomes were better in the patients treated with alternative regimens than in those treated with gemcitabine. Thus, we concluded that use of alternative chemotherapy regimens may be a reasonable strategy for recurrent disease detected within a short period after completion of adjuvant chemotherapy, although additional analyses may be needed in this era of use of FOLFIRINOX and gemcitabine plus nab-paclitaxel.

Surgery for distant recurrences

Recent rapid advances in imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI) have facilitated identification of small-volume metastatic recurrences after resection in cancer patients, and the concept and clinical significance of oligometastases has been established recently in patients with certain cancers, including pancreatic cancer. Damanakis *et al.* proposed defining oligometastatic disease in pancreatic cancer as a limited disease with ≤4 metastases in the liver or lung, together with baseline CA 19-9 levels of <1,000 U/mL, and a treatment response of complete/partial response or stable disease to first-line chemotherapy (48). They reviewed the data of 128 patients with metastatic pancreatic cancer who had never undergone surgery for either the primary tumor or metastases, and identified 10 (7.8%) patients who fulfilled the criteria of oligometastatic disease. All these 10 patients survived for significantly longer periods than the remaining patients; the median overall survival was 19.4 months in this small subgroup *vs.* 7.2 months in the remaining patients [95% confidence interval (CI): 5.7–9.8; P=0.009], and they concluded that patients fulfilling the criteria for oligometastatic disease could potentially benefit from surgical resection.

Recent reports suggest more favorable outcomes in pancreatic cancer patients with isolated pulmonary metastases than in patients with metastases in other locations, although the precise reason for this difference remains unclear. Guerra *et al.* conducted a systematic review/meta-

analysis to evaluate the outcomes in pancreatic cancer patients with isolated pulmonary *vs.* non-pulmonary metastasis (49). The analysis included the data of 11,916 pancreatic cancer patients with isolated distant metastases from 15 primary reports. Of the 11,916 patients, 2,619 patients (22%) had developed recurrence following resection and the remaining 7,884 patients with single-site distant metastasis had not undergone resection. In the setting of single-organ dissemination, patients with isolated lung metastasis showed significantly better survival than those with hepatic, locoregional, or peritoneal recurrence. In particular, patients who developed isolated recurrence in the lung after pancreatectomy showed significantly better outcomes than those who developed isolated locoregional, hepatic or peritoneal relapse after pancreatectomy, in terms of the disease-free survival (15.9 months in patients with isolated pulmonary metastasis *vs.* 12.3, 7.3, and 8.5 months, respectively, in patients with locoregional, hepatic and peritoneal recurrence), survival after recurrence (16.5 *vs.* 9.7, 8, and 5.5 months, respectively), as well as overall survival (34.7 *vs.* 23.6, 11.3, and 17.9 months, respectively). Zheng *et al.* reported that lung metastasis as the initial site of recurrence after pancreatic resection was associated with an earlier tumor stage, lower histologic grade, lower frequency of vascular invasion, and lower residual tumor volume as compared to liver metastasis (50). Recent basic studies conducted to examine the evolution of pancreatic cancer at the genetic level have shown that the clonal complexity of metastatic pancreatic cancer is already existent within the primary tumors, and that organ-specific metastases are derived from different tumor subclones (51,52). The NCCN guidelines include preliminary data to suggest that pulmonary metastasectomy may be advantageous in pancreatic cancer patients presenting with isolated pulmonary metastases after primary resection, although they also state that more data are needed before any definitive recommendations can be made in regard to the management of pancreatic cancer patients with isolated pulmonary metastases.

Conclusions

Despite the recent improvements in surgical techniques and introduction of potentially effective adjuvant treatments for patients with resectable pancreatic cancer, most patients still develop locoregional and/or systemic recurrence after surgery. Although no uniform consensus based on high-level evidence exists as to which intervention might be the most appropriate for such patients, systemic chemotherapy has been used as the main treatment option for patients with distant recurrences, and more recently, even for patients with local recurrence alone, and some regimens have been clearly demonstrated to offer a survival benefit in patients with recurrent pancreatic cancer. For patients with local recurrences alone, local therapies, such as repeat surgical resection and combined chemoradiotherapy have been attempted, although the prognosis of these patients remains dismal and any significant benefits of these therapeutic strategies have yet to be confirmed. Therefore, it is important to consider the patient's quality of life while selecting the appropriate treatment strategy for recurrent pancreatic cancer.

Finally, I would like to emphasize that recently, attempts have been made to establish neoadjuvant therapies to improve the outcomes after surgery, and if successful, could lead to a radical change in the therapeutic strategy for pancreatic cancer (53,54). Although no global standard has been established yet, the potential advantages of neoadjuvant therapy are that it could (I) improve the chances of curative resection by shrinking the primary lesion, (II) exert therapeutic effect against microscopic distant metastases that are difficult to detect by imaging, and (III) allow better selection of patients for curative resection by allowing those showing rapid tumor progression or worsening of the general condition during neoadjuvant therapy to be excluded.

Thus, there is an urgent need for prospective trials to establish the most appropriate perioperative treatment strategies for patients with pancreatic cancer.

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References

1. Mann O, Strate T, Schneider C, et al. Surgery for advanced and metastatic pancreatic cancer--current state and perspectives. Anticancer Res 2006;26:681-6.
2. Barugola G, Partelli S, Marcucci S, et al. Resectable pancreatic cancer: who really benefits from resection? Ann Surg Oncol 2009;16:3316-22.
3. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 1999;230:776-82; discussion 782-4.
4. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267-77.
5. Ueno H, Kosuge T, Matsuyama Y, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. Br J Cancer 2009;101:908-15.
6. Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol 2011;18:1319-26.
7. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200-10.
8. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet 2016;388:248-57.
9. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet 2017;389:1011-24.
10. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med 2018;379:2395-406.
11. Griffin JF, Smalley SR, Jewell W, et al. Patterns of failure after curative resection of pancreatic carcinoma. Cancer 1990;66:56-61.
12. Westerdahl J, Andrén-Sandberg A, Ihse I. Recurrence of exocrine pancreatic cancer--local or hepatic?

Hepatogastroenterology 1993;40:384-7.
13. Sperti C, Pasquali C, Piccoli A, et al. Recurrence after resection for ductal adenocarcinoma of the pancreas. World J Surg 1997;21:195-200.
14. Van den Broeck A, Sergeant G, Ectors N, et al. Patterns of recurrence after curative resection of pancreatic ductal adenocarcinoma. Eur J Surg Oncol 2009;35:600-4.
15. Zhang Y, Frampton AE, Kyriakides C, et al. Loco-recurrence after resection for ductal adenocarcinoma of the pancreas: predictors and implications for adjuvant chemoradiotherapy. J Cancer Res Clin Oncol 2012;138:1063-71.
16. Kolbeinsson H, Hoppe A, Bayat A, et al. Recurrence patterns and postrecurrence survival after curative intent resection for pancreatic ductal adenocarcinoma. Surgery 2021;169:649-54.
17. Nimura Y, Nagino M, Takao S, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepatobiliary Pancreat Sci 2012;19:230-41.
18. Jang JY, Kang JS, Han Y, et al. Long-term outcomes and recurrence patterns of standard versus extended pancreatectomy for pancreatic head cancer: a multicenter prospective randomized controlled study. J Hepatobiliary Pancreat Sci 2017;24:426-33.
19. Wang Z, Ke N, Wang X, et al. Optimal extent of lymphadenectomy for radical surgery of pancreatic head adenocarcinoma: 2-year survival rate results of single-center, prospective, randomized controlled study. Medicine (Baltimore) 2021;100:e26918.
20. Hattangadi JA, Hong TS, Yeap BY, et al. Results and patterns of failure in patients treated with adjuvant combined chemoradiation therapy for resected pancreatic adenocarcinoma. Cancer 2009;115:3640-50.
21. Kleeff J, Reiser C, Hinz U, et al. Surgery for recurrent pancreatic ductal adenocarcinoma. Ann Surg 2007;245:566-72.
22. Arnaoutakis GJ, Rangachari D, Laheru DA, et al. Pulmonary resection for isolated pancreatic adenocarcinoma metastasis: an analysis of outcomes and survival. J Gastrointest Surg 2011;15:1611-7.
23. Thomas RM, Truty MJ, Nogueras-Gonzalez GM, et al. Selective reoperation for locally recurrent or metastatic pancreatic ductal adenocarcinoma following primary pancreatic resection. J Gastrointest Surg 2012;16:1696-704.
24. Strobel O, Hartwig W, Hackert T, et al. Re-resection for isolated local recurrence of pancreatic cancer is feasible, safe, and associated with encouraging survival. Ann Surg Oncol 2013;20:964-72.
25. Miyazaki M, Yoshitomi H, Shimizu H, et al. Repeat pancreatectomy for pancreatic ductal cancer recurrence in the remnant pancreas after initial pancreatectomy: is it worthwhile? Surgery 2014;155:58-66.
26. Boone BA, Zeh HJ, Mock BK, et al. Resection of isolated local and metastatic recurrence in periampullary adenocarcinoma. HPB (Oxford) 2014;16:197-203.
27. Shima Y, Okabayashi T, Kozuki A, et al. Completion pancreatectomy for recurrent pancreatic cancer in the remnant pancreas: report of six cases and a review of the literature. Langenbecks Arch Surg 2015;400:973-8.
28. Chang SC, Hsu CP, Tsai CY, et al. Selective reoperation after primary resection as a feasible and safe treatment strategy for recurrent pancreatic cancer. Medicine (Baltimore) 2016;95:e4191.
29. Yasukawa M, Kawaguchi T, Kawai N, et al. Surgical Treatment for Pulmonary Metastasis of Pancreatic Ductal Adenocarcinoma: Study of 12 Cases. Anticancer Res 2017;37:5573-6.
30. Nakayama Y, Sugimoto M, Gotohda N, et al. Efficacy of completion pancreatectomy for recurrence of adenocarcinoma in the remnant pancreas. J Surg Res 2018;221:15-23.
31. Yamada S, Kobayashi A, Nakamori S, et al. Resection for recurrent pancreatic cancer in the remnant pancreas after pancreatectomy is clinically promising: Results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. Surgery 2018;164:1049-56.
32. Groot VP, Blair AB, Gemenetzis G, et al. Isolated pulmonary recurrence after resection of pancreatic cancer: the effect of patient factors and treatment modalities on survival. HPB (Oxford) 2019;21:998-1008.
33. Kim YI, Song KB, Lee YJ, et al. Management of isolated recurrence after surgery for pancreatic adenocarcinoma. Br J Surg 2019;106:898-909.
34. Moletta L, Serafini S, Valmasoni M, et al. Surgery for Recurrent Pancreatic Cancer: Is It Effective? Cancers (Basel) 2019;11:991.
35. Serafini S, Sperti C, Friziero A, et al. Systematic Review and Meta-Analysis of Surgical Treatment for Isolated Local Recurrence of Pancreatic Cancer. Cancers (Basel) 2021;13:1277.
36. Miyasaka Y, Ohtsuka T, Matsuda R, et al. High-risk

lesions in the remnant pancreas: fate of the remnant pancreas after pancreatic resection for pancreatic cancer and intraductal papillary mucinous neoplasms. Surg Today 2020;50:832-40.
37. Hashimoto D, Chikamoto A, Ohmuraya M, et al. Pancreatic cancer in the remnant pancreas following primary pancreatic resection. Surg Today 2014;44:1313-20.
38. Sunagawa H, Mayama Y, Orokawa T, et al. Laparoscopic total remnant pancreatectomy after laparoscopic pancreaticoduodenectomy. Asian J Endosc Surg 2014;7:71-4.
39. Sahakyan MA, Yaqub S, Kazaryan AM, et al. Laparoscopic Completion Pancreatectomy for Local Recurrence in the Pancreatic Remnant after Pancreaticoduodenectomy: Case Reports and Review of the Literature. J Gastrointest Cancer 2016;47:509-13.
40. Nakagawa Y, Fukami Y, Harada T, et al. Laparoscopic pancreaticoduodenectomy for remnant pancreatic recurrence after laparoscopic distal pancreatectomy and hepatectomy for greater omentum leiomyosarcoma. Asian J Endosc Surg 2020;13:117-20.
41. Kyaw PPP, Goh BKP. Robotic assisted laparoscopic completion pancreatectomy for recurrent intraductal papillary mucinous neoplasm after previous open pancreatoduodenectomy: A case report and literature review. Ann Hepatobiliary Pancreat Surg 2019;23:206-9.
42. Wilkowski R, Thoma M, Bruns C, et al. Combined chemoradiotherapy for isolated local recurrence after primary resection of pancreatic cancer. JOP 2006;7:34-40.
43. Nakamura A, Itasaka S, Takaori K, et al. Radiotherapy for patients with isolated local recurrence of primary resected pancreatic cancer. Prolonged disease-free interval associated with favorable prognosis. Strahlenther Onkol 2014;190:485-90.
44. Zhu X, Cao Y, Liu W, et al. Stereotactic body radiotherapy plus pembrolizumab and trametinib versus stereotactic body radiotherapy plus gemcitabine for locally recurrent pancreatic cancer after surgical resection: an open-label, randomised, controlled, phase 2 trial. Lancet Oncol 2021;22:1093-102.
45. Groot VP, van Santvoort HC, Rombouts SJ, et al. Systematic review on the treatment of isolated local recurrence of pancreatic cancer after surgery; re-resection, chemoradiotherapy and SBRT. HPB (Oxford) 2017;19:83-92.
46. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Pancreatic Adenocarcinoma. 2021 [cited 2021 June 20]. Available online: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf
47. Taniyama TK, Morizane C, Nakachi K, et al. Treatment outcome for systemic chemotherapy for recurrent pancreatic cancer after postoperative adjuvant chemotherapy. Pancreatology 2012;12:428-33.
48. Damanakis AI, Ostertag L, Waldschmidt D, et al. Proposal for a definition of "Oligometastatic disease in pancreatic cancer". BMC Cancer 2019;19:1261.
49. Guerra F, Barucca V, Coletta D. Metastases or primary recurrence to the lung is related to improved survival of pancreatic cancer as compared to other sites of dissemination. Results of a systematic review with meta-analysis. Eur J Surg Oncol 2020;46:1789-94.
50. Zheng B, Ohuchida K, Yan Z, et al. Primary Recurrence in the Lung is Related to Favorable Prognosis in Patients with Pancreatic Cancer and Postoperative Recurrence. World J Surg 2017;41:2858-66.
51. Campbell PJ, Yachida S, Mudie LJ, et al. The patterns and dynamics of genomic instability in metastatic pancreatic cancer. Nature 2010;467:1109-13.
52. Kim MS, Zhong Y, Yachida S, et al. Heterogeneity of pancreatic cancer metastases in a single patient revealed by quantitative proteomics. Mol Cell Proteomics 2014;13:2803-11.
53. Unno M, Motoi F, Matsuyama Y, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP-05). J Clin Oncol 2019;37:abstract 189.
54. Versteijne E, Suker M, Groothuis K, et al. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. J Clin Oncol 2020;38:1763-73.

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