

Multimodality treatment of recurrent pancreatic cancer: Mith or reality?

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Abstract

Pancreatic adenocarcinoma is the fourth cause of cancer-related death in the United States. Surgery is the only potentially curative treatment, but most patients present at diagnosis with unresectable or metastatic disease. Moreover, even with an R0 resection, the majority of patients will die of disease recurrence. Most recurrences

occur in the first 2-year after pancreatic resection, and are commonly located in the abdomen, even if distant metastases can occur. Recurrent pancreatic adenocarcinoma remains a significant therapeutic challenge, due to the limited role of surgery and radio-chemotherapy. Surgical management of recurrence is usually unreliable because tumor relapse typically presents as a technically unresectable, or as multifocal disease with an aggressive growth. Therefore, treatment of patients with recurrent pancreatic adenocarcinoma has historically been limited to palliative chemotherapy or supportive care. Only few data are available in the Literature about this issue, even if in recent years more studies have been published to determine whether treatment after recurrence have any effect on patients outcome. Recent therapeutic advances have demonstrated the potential to improve survival in selected patients who had undergone resection for pancreatic cancer. Multimodality management of recurrent pancreatic carcinoma may lead to better survival and quality of life in a small but significant percentage of patients; however, more and larger studies are needed to clarify the role of the different therapeutic options and the optimal way to combine them.

Key words: Multimodality treatment; Pancreas; Pancreatic neoplasms; Pancreatectomy; Tumor's recurrence

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Core tip: Different therapeutic options are available for the treatment of patients with pancreatic adenocarcinoma recurrence, even if only few data have been reported in the Literature on their effective benefit for patients' outcome. In this work we present the current English Literature about this issue, the possible indications for the different therapeutic options and the available data on patients' outcome.

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INTRODUCTION

Pancreatic adenocarcinoma is the fourth most common cause of cancer-related death among men (after lung, prostate, and colorectal cancer) and women (after lung, breast, and colorectal cancer) in the United States^[1]. The incidence of pancreatic adenocarcinoma has been increasing in United States while mortality rates have remained largely unchanged^[1]. Surgery is the only potentially curative treatment for pancreatic cancer (PC), with a median survival after pancreatic resection of 12.6 mo^[2]. There are no effective screening strategies for this tumor and most patients present at diagnosis with unresectable or metastatic disease. Moreover, the majority of patients who undergo surgical resection will die of disease recurrence, with a 3-year disease-specific survival of only 27%^[3]. In fact, even after an R0 resection, most patients will experience a cancer recurrence, either as isolated local recurrence, hepatic metastasis or peritoneal dissemination^[4]. Most recurrences occur within 2 years of surgery, and are mainly located in the abdomen^[5], even if lung and bone metastases can also occur. Recurrent PC remains a significant therapeutic challenge, due to the advanced stage and the limited role of surgery and radio-chemotherapy. So, nihilistic attitude is frequent among clinicians towards PC relapse. In other primary malignancies, such as colorectal cancer, neuroendocrine carcinomas, renal cell carcinoma, resection of recurrent disease can be curative in selected patients^[6-8]. On the other hand, surgical management of recurrent PC is usually unfeasible because tumor's relapse typically presents as unresectable, multifocal disease with an aggressive growth^[5]. Therefore, treatment of patients with recurrent pancreatic adenocarcinoma has historically been limited to palliative chemotherapy or supportive care. Despite the extremely high rate of tumor relapse, no evidenced-based guidelines for post-surgical follow-up exist. Standard surveillance usually includes clinical examination, serum Carbohydrate Antigen 19-9 (CA 19-9) determination and radiological studies [*i.e.*, ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and chest X-ray]. The National Comprehensive Cancer Networks (NCCN) guidelines for follow-up after surgery recommend a physical examination, CA 19-9 determination and CT scan of the abdomen and pelvis every 3-6 mo for 2 year and then annually^[9]. However, the value of follow-up in detecting early recurrence and its impact on survival or quality of life of patients has not been clearly determined. Moreover, no treatment has had any strong impact on recurrent PC to date, so the need for a close follow-up is argued. In fact, if an earlier

identification of tumor relapse can give indication for further investigational studies, there are no available data showing that earlier recurrence's treatment leads to better patients outcome^[9]. However, detection of recurrence in asymptomatic patients has been shown to significantly improve survival in comparison to symptomatic patients^[10]. So, detection of asymptomatic relapse may facilitate investigational studies for appropriate treatments. On the contrary, it has been reported that increasing the frequency and intensity of postoperative follow-up (*i.e.*, CT scan) increases cost but not produces survival advantage^[11]. According to ESMO Guidelines^[12], due to the impossibility of cure a pancreatic recurrence, "a follow-up schedule should be discussed with the patient and designed to avoid emotional stress and economic burden for the patient". Only few data are available in the Literature about this issue, even if in recent years more studies have been published to determine whether treatment after recurrence have any effect on patients outcome. Recent therapeutic advances have demonstrated the potential to improve survival in selected patients, but more and larger studies are needed to argue the role of the different therapeutic options and the optimal way to combine them. So, in order to improve the management of patients with recurrent pancreatic tumor after initial resection, some crucial points have to be considered: (1) which is the best method to follow and detect as soon as possible tumor's relapse? (2) is there a place for surgery in recurrent PC? (3) which is the best treatment for tumor's recurrence, and how to combine different therapeutic strategies?

DETECTION OF RECURRENCE

Post-surgical surveillance of PC include serum Carbohydrate Antigen 19-9 (CA 19-9) determination and radiological studies. CA 19-9 is the only biomarker for pancreatic adenocarcinoma approved by FDA and the most widely studied^[13]. The estimated sensitivity and specificity of CA 19-9 for the diagnosis of PC are respectively 71%-81% and 83%-90% (cut-off level of 37 U/mL)^[14,15]. A part from its diagnostic utility, CA 19-9 has also a role in predicting cancer recurrence after surgical resection and it is routinely used in post-surgical follow-up of resected patients. Preoperative CA 19-9 levels have been investigated as predictors of tumor recurrence. Sugiura *et al*^[16] found that a preoperative CA 19-9 value ≥ 100 U/mL was a significant predictor of early recurrence and of a poor prognosis after resection for pancreatic adenocarcinoma. After a curative surgical resection, CA 19-9 levels are expected to decrease and return to a normal range. CA 19-9 postoperative elevations precede clinical/radiological evidence of recurrence by 2-6 mo^[17]. Some studies have investigated the correlation of postoperative CA 19-9 levels and the rate of recurrence. Hata *et al*^[18] found a statistical relationship between postoperative CA 19-9 > 37 U/mL and the rate of disease recurrence. Patients

with postoperative elevated CA 19-9 had an overall recurrence rate significantly higher than patients with normalized postoperative CA 19-9. In the experience of Park *et al.*^[19] post-treatment CA 19-9 and normalization of postoperative CA 19-9 were independent prognostic markers both for disease-free and overall survival. However, the utility of CA 19-9 is limited by the fact that it is not expressed in 5%-10% of population and that it can be falsely elevated in the presence of biliary obstruction^[20]. In recent years other gene and molecular biomarkers have been investigated in the early detection of PC recurrence. Matakı *et al.*^[21] investigated the role of blood circulating tumor cells (CTCs) as an early predictor of tumor relapse after PC curative resection. In particular Carcinoembryonic Antigen (CEA) mRNA expression using RT-PCR was evaluated in blood samples of 53 PC resected patients. CEA mRNA sensitivity and specificity were respectively 75% and 94% in predicting tumor recurrence^[21]. Further studies are needed to find accurate and feasible biomarkers for predicting early disease recurrence. Contrast-enhanced CT scanning is the standard radiological study performed in post-surgical follow-up of PC. However, differentiation of post-treatment recurrent or residual tumor from fibrosis or post-surgical alterations is difficult with conventional imaging techniques. After pancreaticoduodenectomy for PC, postoperative changes in the areas around the common hepatic artery and proximal superior mesenteric artery are commonly recognized^[20]. These sites are also common areas of tumor recurrence, and it may be a diagnostic problem to differentiate postoperative alterations from recurrent disease^[22]. Postoperative complications (cholangitis, pancreatic or biliary fistula, abdominal fluid collections) can contribute to the development of fibrosis or post-surgical alterations^[23]. Since fibrosis is present in both adenocarcinomas and postoperative changes, the enhancement pattern may not be helpful, because both benign and malignant recurrent tissue may show delayed contrast enhancement^[24]. Therefore, differential diagnosis between postoperative change from recurrence is difficult on a single CT study. Moreover, a reactive mesenteric lymphadenopathy can be present for years after surgery, and it is impossible to differentiate from lymph node metastases: only a progressive increase in lymph node size or the association with a recurrent mass can suggest the presence of lymph node metastases^[25]. Recently some Authors have demonstrated the usefulness of PET/CT for restaging and detection of recurrence of PC^[26,27]. Kitajima *et al.*^[27] analyzed forty-five patients previously treated for PC underwent PET/CT for suspected recurrence. The sensitivity of PET/contrast-enhanced CT in detecting local recurrence, abdominal lymph node metastasis, and peritoneal dissemination were 83.3%, 87.5%, and 83.3% respectively^[27]. PET detects tumor relapse earlier compared with CT, and influences treatment strategies in a significant percentage of patients. In a previous work, we studied the role of 18-FDG PET in

detecting tumour relapse after PC resection in a series of 72 patients^[28]. In that study, FDG-PET showed tumor recurrence in 28 patients with negative or inconclusive CT, enabling chemoradiotherapy to be started in 15 patients and the resection of recurrent disease in six^[28]. Moreover, preoperative maximum standardized uptake value (SUV) seems predictive of PC recurrence in the early post-operative period^[29]. Okamoto *et al.*^[29] studied SUV values obtained in preoperative FDG-PET and compared them between patients with and without PC recurrence within the first six postoperative months. They found that preoperative SUV was higher in the recurrence group of patients and that a high preoperative SUV was an independent risk factor for early tumor relapse after surgery. Thus, FDG-PET may play a crucial role in predicting and detecting postoperative tumor relapse after PC resection. The ideal timing for postoperative FDG-PET is not well defined, but it may be suggested to perform it 4-6 mo after surgery and at least 1.5 mo after any adjuvant therapy^[28].

THE ROLE OF SURGERY FOR RECURRENT PC

Different patterns of recurrent PC have been described: locoregional recurrence (lymph node metastases, tumor relapse in the bed of pancreatic resection, tumor recurrence in the pancreatic remnant), distant metastases (liver, lung, bone) or peritoneal dissemination. Hepatic metastases seems to have a worse prognosis when compared to local recurrence^[30,31]. Surgery for recurrent PC has been usually limited to solve gastrointestinal or biliary obstruction, being the morbidity and mortality expected for this kind of surgery high and the benefit for patients unclear. Re-resection of PC relapse is reported only as single case reports or in small series. Therefore, the clinical outcome of patients undergoing surgery for PC recurrence is not known. Even if PC recurrence has commonly be considered a systemic disease, several cases of isolated local recurrence have been reported^[32]. Redo surgery for local recurrence (Table 1^[4,33-39]) can consist in different surgical approaches, such as local dissection of lymph nodes, exeresis of soft tissue on the pancreatic bed or completion pancreatectomy of the remnant pancreas^[4]. Strobel *et al.*^[32] reported a series of 105 patients undergoing operative expiration for suspected isolated local PC recurrence. Among these patients, 57 isolated local recurrence were intraoperatively confirmed and 41 resections were performed. Patients with confirmed isolated local recurrence had a longer median survival compared to patients with intraoperative finding of metastases (16.4 mo vs 9.4 mo)^[32]. Moreover, a significantly longer survival was observed in the resected patients compared with the subgroup without resection due to local irresectability^[32]. Lavu *et al.*^[33] reported a series of 11 patients (6 histologically proven) who underwent completion pancreatectomy for recurrence:

Table 1 Review of recent works on redo surgery for ductal adenocarcinoma local recurrence

Ref.	Year	n	DFI (mo)	Site of recurrence	Surgery	Associated procedure	Morbidity	Mortality	SPR	OS
Dalla Valle <i>et al</i> ^[36]	2006	1	18	1 panc remnant	1 RP	Distal gastrectomy, segmentary resection of transverse colon, splenectomy, extended lymph node dissection	0	0	24	42
Kleeff <i>et al</i> ^[35]	2007	12	13	8 local 2 local + stomach 2 local + mesentery	11 resection 1 partial gastrectomy	4 IORT 1 right hemicolectomy	NA	NA	13	NA
Koizumi <i>et al</i> ^[37]	2010	2	83 28	2 panc remnant	2 RP	/	NA	0	10 8	93 36
Lavu <i>et al</i> ^[33]	2011	8	27.5	8 panc remnant	8 RP	1 subtotal gastrectomy	(2/8) 25%	0	15	74
Thomas <i>et al</i> ^[34]	2012	7	41.1	1 abdominal wall 5 panc remnant 1 resection bed	2 resection 5 RP	NA	NA	0	NA	79.3
Kobayashi <i>et al</i> ^[38]	2012	1	36	1 panc remnant	1 RP	Partial pancreas autotransplantation	0	0	20	
Boone <i>et al</i> ^[39]	2013	10	25.3	3 resection bed 2 panc remnant, small bowel 1 panc remnant, colon 1 panc remnant, small bowel, stomach 3 stomach	3 resection pancreatic bed mass 4 RP 2 partial gastrectomy 1 SBR	3 SBR 1 partial gastrectomy + splenectomy 1 partial colectomy	NA	0	32.4	59.1
Miyazaki <i>et al</i> ^[4]	2014	11	32	11 panc remnant	11 RP	1 celiac resection + total gastrectomy 1 portal vein resection	(3/11) 27%	0	25	78.2
Total		62	27.5 (me)				/	0	17.5 (me)	66.55 (me)

DFI: Disease free interval (from primary pancreatic resection); RP: Repeat pancreatectomy; SBR: Small bowel resection; SPR: Survival post-reoperation; OS: Overall survival after initial pancreatectomy; NA: Not applicable; me: Median; IORT: Intraoperative radiation therapy.

The median survival after redo surgery was 32 mo with no postoperative mortality. Miyazaki *et al*^[4] published a series of 11 patients undergoing repeated pancreatectomy for isolated local recurrence in the remnant pancreas: Survival after initial pancreatectomy was better in the repeated pancreatectomy group when compared to patients with unresectable recurrence (78.2 mo vs 20.3 mo). Thomas *et al*^[34] published a series of 21 patients undergoing reoperation for pancreatic recurrence. Patients were selected for surgery according to the recurrence pattern: Patients with carcinomatosis or multiple sites of recurrence were excluded, while local recurrence, one single site of distant recurrence and regional recurrence (as a solitary abdominal wall implant) were considered for surgery^[34]. In this series, patients with an initial disease-free interval > 20 mo had a longer median survival than those who did not. Kleeff *et al*^[35] reported a survival benefit in patients with a longer disease free interval from primary resection longer than 9 mo. Some studies reported surgical metastasectomy of isolated liver and lung metastases after surgical resection of primary PC (Table 2^[34,35,39,40]). Arnaoutakis *et al*^[40] published a series of 9 patients undergoing metastasectomy of solitary lung metastasis, with a longer overall survival (51 mo vs 23 mo) in comparison to patients who did not receive surgery. The majority of these studies consists of small series

of patients, without a true control group, so a general recommendation on redo surgery for PC recurrence cannot be given. However, the available data indicate a potential survival benefit after resection in selected patients. The low morbidity and mortality rates after reoperation reported in the published studies underline the feasibility of this kind of surgery in high volume centers. A careful patients selection plays a crucial role for considering re-resection of pancreatic recurrence. In fact, selecting patients with indolent surgical disease may be the key to give a survival benefit. In particular, patients with a good performance status, with a solitary surgically resectable location of recurrence, and with a relatively long disease free interval from primary pancreatic resection seem to benefit from redo surgery. Moreover, in re-resection for isolated local recurrence an R0 resection must be the goal to obtain a favorable prognosis. Regarding lung metastases, even if it seems that surgical resection in selected patients may be considered therapeutical options, more studies are needed to verify the true survival benefit in these patients. Another issue to focus on may be quality of life: Surgical re-resection could be considered not only for prolonged survival purpose, but also for symptoms palliation. Finally, surgery for recurrent PC has to be embedded in multimodality treatment of these patients, together with preoperative treatment, adjuvant or

Table 2 Review of recent works on redo surgery for ductal adenocarcinoma metastatic recurrence

Ref.	Year	n	DFI (mo)	Site of recurrence	Surgery	Associated procedure	Morbidity	Mortality	SPR	OS
Kleeff <i>et al</i> ^[35]	2007	2	15.5	2 liver	1 left hemihepatectomy 1 right hemihepatectomy	/	NA	NA	23.5	NA
Arnaoutakis <i>et al</i> ^[40]	2011	9	34	9 lung	10 lung resection	/	1 AF	0	18.6	51
Thomas <i>et al</i> ^[34]	2012	14	52.4 (LR) 7.6 (LiR)	1 brain 6 liver 7 lung	4 RFA 10 resection	/	NA	0	NA	92.3 (LR); 32.5 (LiR)
Boone <i>et al</i> ^[39]	2013	12	34.35 (LR) 17 (LiR) 7.6 (Ovary)	6 liver 5 lung 1 ovary	4 liver resection 2 RFA 5 lung resection 1 hysterectomy + BSO	2 RFA	NA	0	20.1 (LR) 13.9 (LiR) 12.7 (ovary)	70.8 (LR) 29.8 (LiR) 20.3 (ovary)
Total		37	25.5 (me)	14 liver 21 lung 1 brain 1 ovary				0	18.6 (me)	41.75 (me)

DFI: Disease free interval; SPR: Survival post-reoperation; OS: Overall survival; LR: Lung recurrence; LiR: Liver recurrence; AF: Atrial fibrillation; RFA: Radiofrequency ablation; BSO: Bilateral salpingo-oophorectomy; NA: Not applicable; me: Median.

palliative treatment. More studies are needed to define the clinical outcome of pancreatic re-resection, in combination with other therapeutical modalities.

CHEMORADIOTHERAPY

Limited information is available regarding the importance of chemoradiation applied in local or distant recurrence of PC. In 2006, Wilkowski *et al*^[41] published a series of 18 patients with local metastases after surgical treatment of PC and treated with chemioradiotherapy. Five patients treated with Gemcitabine had a longer mean survival compared to four untreated patients (22.3 mo vs 6.6 mo). This was the first study suggesting that chemoradiotherapy could be an effective option in recurrent PC. In 2003 an open phase I study on the feasibility of a combination therapy consisting of 5-FU/leucovorin plus oxaliplatin and irinotecan (FOLFIRINOX) for the treatment of patients with metastatic solid tumors was published^[42]. The study showed anti-tumor activity in two patients with PC. Later II phase trials specifically addressed patients with advanced and metastatic PC, showing promising results^[43,44]. The randomized phase III PRODIGE trial evaluated FOLFIRINOX versus gemcitabine alone in patients with metastatic PC and good performance status: A dramatic improvement in both median progression-free survival and median overall survival in favour of the group receiving FOLFIRINOX was seen^[45]. Very recently, a phase III clinical trial showed the efficacy of the combination nab-paclitaxel and gemcitabine to improve overall survival compared to gemcitabine alone for metastatic PC^[46]. Limitation to these chemotherapy regimens is mainly due to their significant toxicity (neutropenia, thrombocytopenia, sensory neuropathy). Therefore, a balance between side effects and the significant but limited benefit offered by these chemotherapeutic regimens must be done together with the patient and his family. According to NCCN guidelines for recurrent PC, chemoradiation can be considered in patients with local recurrence only^[47].

For patients with metastatic disease (with or without local recurrence), treatment decisions are influenced by the time interval between the end of adjuvant therapy to the diagnosis of metastases. If the interval time is less than 6 mo, an alternative chemotherapy option can be administered^[47]. If it is greater than 6 mo, both previously administered systemic therapy and an alternative systemic regimen can be considered^[47]. Recommended systemic regimens are the same as for second-line therapy in metastatic disease: Gemcitabine or gemcitabine-based combination therapy for patients previously treated with fluoropyrimidine-based therapy or fluoropyrimidine-based therapy for patients previously treated with gemcitabine-based therapy^[47]. Conventional radiotherapy shows unsatisfactory local control because therapeutic radiation dose to the pancreatic tumor is limited by the sensitivity of surrounding tissues^[48]. The cyberknife system, used since 2001 to liver radiation in any human radiosensitive tumor, seems to overcome this problem^[49]. With the assistance of PET and CT Scan, Cyberknife offers a stereotactic boost of radiation alone or in combination with conventional radiation therapy. Although survival is determined primarily by a systemic control, local control is an important factor contributing to quality of life (pain control, prevention of gastric outlet obstruction)^[50]. One more therapeutic option is given by radiofrequency ablation (RFA). RFA has shown to improve survival in patients with locally advanced unresectable PC^[51,52]. Some studies have focused on the role of RFA in the treatment of liver metastases from PC. Park *et al*^[53] performed RFA on 34 patients with liver metastases from PC: In oligometastatic patients they found an improved survival after RFA compared to patients without liver metastases and no treatment. Available data on chemoradiotherapy, cyberknife and RFA are few and derives from small series of patients. Larger randomized trial are needed in order to define the effective benefit of such therapeutic regimens, the best timing to start treating a patient and the best way to combine the different therapeutic options.

CONCLUSION

Even if few data are available in the Literature, multimodality approach to PC recurrence seems to offer a good palliation in a significant percentage of patients. Radical resection of recurrent tumor may be achievable in very selected patients who had undergone pancreatectomy for PC. Prolonged survival is possible in this subset of patients comparing to those receiving chemoradiotherapy or supportive care. Moreover, the combination of standard therapies (*i.e.*, chemoradiotherapy, surgery) with new treatment modalities (*i.e.*, RFA, Stereotactic radiotherapy, electroporation) may open a new window on an otherwise devastating disease. An accurate follow-up is thus warranted in order to improve the management of recurrent tumor. More studies are needed in order to better define clinical outcome of patients, timing for therapeutical approach and the way to combine surgery with other therapeutic options.

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