Review

Surgery for Advanced and Metastatic Pancreatic Cancer – Current State and Perspectives

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Abstract. Advanced disease, defined as vascular invasion or invasion into adjacent organs, in pancreatic ductal adenocarcinoma still remains a major diagnostic and therapeutic challenge. In most cases, only exploratory laparotomy will ultimately ensure surgical resectibility. A physician is ill-advised to make any decision regarding palliation relying on CT-scan, MRI, ultrasonography or angiography, since vascular invasion is difficult to diagnose because of peritumoral pancreatitis mimicking vascular invasion. Only in the case of complete vascular encasement of the mesenterico-portal axis or celiac trunk is a laparotomy unnecessary. If a T3 lesion is present, the patient will benefit greatly from R0 surgical resection, even if this includes en bloc resections of the transverse colon, or the portal vein, which can be reconstructed without vascular grafting in most cases. In the presence of distant metastases only palliative treatment is useful. If liver metastases are identified pre-operatively, palliation should include endoscopic common bile duct stenting in the presence of icterus, or endoscopic duodenal stenting in the case of percutaneous endoscopic gastrostomy. If metastases are found during exploratory laparotomy, surgical palliation should be considered (bilio-digestive anastomosis or gastro-enterostomy), since these procedures do not lead to a significantly longer hospital stay and are not associated with significant morbidity or mortality. Pain control can be ensured using morphine analogs, CT-guided sympathectomy or thoracoscopic sympathectomy. Currently, there is no answer as to which option offers the best pain control and quality of life.

There is also an ongoing debate on the palliative Whipple’s procedure, even in the event of single liver metastases, since this procedure is associated with limited mortality (well below 5% in high-volume centers) and ensures excellent pain control. This needs an individual assessment of risk and, furthermore, a detailed discussion with the patient. There are no studies in which resection has been performed as a standard procedure for palliation. This question should be answered in a multicenter randomized trial, otherwise the palliative Whipple’s operation should still be considered experimental, since it is not likely to significantly prolong survival.

Approximately 31,000 people develop pancreatic adenocarcinoma each year in the United States, making it the fourth most common cause of cancer death, with the majority of patients expected to die from the disease (1, 2). To date, surgical resection is the only potentially curative treatment for pancreatic cancer. Unfortunately, because of the late presentation of the disease, only 15 to 20 % of patients are candidates for surgical intervention. The overall median survival is less than 6 months and 5-year overall survival rates of 0.4-4% have been described (3, 4). Between 2.6 and 9% of patients undergo pancreatic resection with a median survival of 11-20 months and a 5-year survival rate of 7-25%. Most treatment failures are due to local recurrence and/or hepatic metastases and occur within 12 to 24 months after surgical intervention (5, 6). Staging is a critical part in the pre-operative management of pancreatic cancer, as for all solid tumors. For pancreatic cancer patients, however, the main goal is to determine the resectability of the tumor. Even with the most effective standard therapies, patients with locally advanced or metastatic pancreatic cancer have a median survival of approximately 10-12 and 4-6 months, respectively (7-9).

Walter Kausch initially described the technique of pancreatoduodenectomy in 1912, which was modified by Allen O. Whipple more than two decades later. Although major advances have been made in the surgical management of
pancreatic cancer since the era of Whipple, the principal goal remains the same: removal of the complete tumor including a systematic lymphadenectomy, without leaving residual tumor.

In the past, major pancreatic surgery, in particular the Whipple operation, was associated with very high morbidity and mortality rates (10, 11), leading to initiatives such as: "Congress should pass a law making it illegal to do a Whipple operation" (Harken, 1986). Many physicians remained sceptical about resection and believed that these patients should not spend their remaining life with serious impairment resulting from surgical measures. However, modern series show that, in experienced hands, the standard Whipple procedure is associated with a 5-year survival of 20 to 30% in completely resected patients with a peri-operative mortality rate of less than 4% (12, 13). This relatively low peri-operative mortality rate represents a decline from over 15% in the 1970s, making the Whipple procedure a much more appealing surgical option, even in patients with advanced disease. Recently, various studies have demonstrated that mortality rates were nearly 4-fold increased on comparing pancreaticoduodenectomies performed in hospitals with less than 1 case per year to those performed in hospitals dealing with more than 16 cases annually (14). Even within high-volume hospitals, the operative mortality rates varied by a factor of nearly 4 to 1 according to the experience of the individual surgeons (15). Against this background of declining morbidity and mortality and improvement of survival, indications for surgical intervention have increased. Thus, pancreatic surgery as a palliative treatment can be considered in carefully selected patients, although only in the context of high-volume centers (16, 17).

Regarding adjuvant therapy, there is no consensus in terms of the optimal management of suitable patients after resection of a pancreatic cancer. Most Europeans support the conclusions of the European Study of Pancreatic Cancer-1 (ESPAC-1) trial, which showed that chemotherapy prolonged survival, while chemo-radiotherapy may be associated with worse survival. Thus, preference has been given to adjuvant chemotherapy alone, after pancreatic cancer resection (18, 19). The choice of chemotherapy and the magnitude of benefit may be further refined by the results of the ESPAC-3 trial, in which patients were randomly assigned to observation, leucovorin-modulated 5-Fluorouracil, or Gemcitabine, after resection of a pancreatic cancer. The American approach to adjuvant therapy differs from that in Europe, with regard to the benefit of chemoradiotherapy (20).

**What is Meant by Advanced Pancreatic Cancer?**

Advanced disease in pancreatic ductal adenocarcinoma, defined as vascular invasion or invasion into adjacent organs, still remains a major diagnostic and therapeutic challenge. In most cases, only exploratory laparotomy will ultimately ensure surgical resectability. Characteristics that predicted or ruled out malignancy would have a great impact on the further diagnostic evaluation and choice of more or less aggressive treatment. As mentioned above, minimized peri-operative morbidity and mortality, as well as improvement of quality of life, are the main aims of any surgical intervention. The crucial question for pre-operative diagnostics is to detect the exact dimensions of the pancreatic malignancy, especially in view of treatment limitations and the abysmal prognosis of established pancreatic cancer. In 1976, Freeny et al. suggested that the presence of a double duct sign on endoscopic retrograde cholangiopancreatography (ERCP) as a co-existent, and adjacent stenosis of the main pancreatic duct and the common bile duct predicts the presence of pancreatic carcinoma, with a sensitivity approaching 100%. However, in numerous recently-published studies, the specificity of the double duct sign in predicting the presence of pancreatic malignancy appeared to be lower than previously reported (21). Kalady et al. retrospectively reported 355 cases with pancreatic duct stenosis diagnosed by ERCP during a 7-year period at a single institution (22). In this series, the sensitivity and specificity for the double duct sign for malignancy were 77% and 80%, respectively, and the positive predictive value was 65%. Predictors of malignancy were statistically similar for both isolated pancreatic duct stenosis and those associated with a common bile duct stricture. Although the most common cause of this presentation is a carcinoma of the head of the pancreas, there are benign causes, including chronic pancreatitis in the majority of cases, as well as primary retroperitoneal fibrosis, Karposi’s sarcoma or even infectious disease (23-25). In most cases, only surgical exploration will ultimately ensure surgical resectability.

**Distant Metastasis**

In the case of pre-operatively recognized distant metastasis (liver, peritoneal carcinosis, lung), verified by histopathological examination, palliative management depends on the individual patient’s symptoms. In the instance of biliary obstruction, the endoscopic approach should be favored. The treatment of gastric or duodenal outlet obstruction should also include endoscopic stenting or percutaneous endoscopic gastrostomy. If endoscopic treatment is not possible, surgical bypass procedures (hepaticojejunostomy and gastrojejunostomy) must be considered to control the condition. If peritoneal carcinosis is detected intra-operatively, a double bypass is the appropriate approach. In the case of liver metastasis undetected pre-operatively, the number, size and the localization of the metastases play an important role. In
patients with a solitary localized liver tumor appropriate for atypical resection, a palliative pancreaticoduodenectomy can be considered as long as an R0 resection is warranted (26).

**Vessel Involvement (V. Mesenterica Superior, Celiac Trunk, Portal Vein)**

Traditionally, tumor involvement of the V. mesenterica superior, celiac trunk or the portal vein have been considered as signs of prognostic irresectability. Despite major advances in pre-operative staging, including computed tomography (CT)-scan, magnetic resonance imaging (MRI), ultrasonography or angiography, it is still difficult to make a decision regarding the pre-operative evaluation of resectability in terms of vascular invasion, because peritumoral pancreatitis mimics vascular invasion. If a T3-lesion is present, the patient will greatly benefit from R0 surgical resection, even if this includes en bloc resection of adjacent organs, such as the transverse colon or the portal vein. It is now well accepted that residual disease is associated with extremely poor outcome.

Various studies have evaluated the patterns of recurrence and survival after pancreaticoduodenectomy with venous resection (V. mesenterica superior/portal vein) (Table I) (2). To date, the predominance of data suggest that, for patients with isolated involvement of the superior mesenteric vein (SMV) or portal vein, pancreaticoduodenectomy and venous resection are associated with survival similar to that of patients who undergo standard pancreaticoduodenectomy alone. The rationale of extending the standard procedure by adding venous resection is to achieve histologically-negative margins with no residual tumor. The presence of tumor invasion into the superior mesenteric artery (SMA) or the celiac trunk remains a contra-indication for pancreaticoduodenectomy, and a less invasive treatment option should be preferred.

**Patients Potentially Eligible for Palliative Resection**

Currently, most palliative resections take place in operations with curative intention when irresectability is established after a "point of no return" or, most commonly, in an R1-situation when the histopathological examination shows microscopically-involved resection margins.

The question that has to be addressed is controversial at present: is there any place for palliative resection in patients with advanced pancreatic cancer? Is it justified to perform a palliative resection in the case of a solitary liver metastasis, if an R0 resection is possible? To date, there have been no studies in which resection has been performed as a routine procedure for palliation. Furthermore, there is no evidence-based data comparing palliative resections with bypass procedures, which were predominantly performed in a palliative situation.
In addition to improved survival (buying time), several additional aspects require consideration regarding palliative resection as a standard procedure. The most important issues, as mentioned above, are peri-operative morbidity and mortality. Additional outcome measures include symptom control (pain, itching, jaundice, gastrointestinal symptoms) and quality of life (QoL). Last, but not least, there should be a minimized need for rehospitalization, irrespective of the individual treatment. These outcome measures, including QoL, morbidity and mortality after palliative resections, must be compared to alternative palliative surgical options such as double-bypass, endoscopic or medical treatment (27). Unfortunately, only limited data are available on QoL after palliative pancreatic surgery (28, 29).

As with pancreatic resection, major advances in non-operative palliation have been made. Obstructive jaundice can be controlled endoscopically or percutaneously in the majority of patients (27). These sophisticated techniques offer alternatives for patients with advanced disease or those unfit for surgery. However, only surgical intervention can control all the major symptoms of pancreatic cancer, including hepaticejunostomy and gastrojejunosnomy for biliary or duodenal obstruction. Furthermore, pain management can be improved with the use of intra-operative chemical splanchniectomy (17).

Yeo et al. demonstrated, in a series of 650 patients, a hospital mortality rate of 1.6% and similar peri-operative morbidities in patients undergoing palliative pancreaticoduodenectomy and traditional surgical palliation. In their experience, pancreaticoduodenectomy was associated with a slightly prolonged operative time and hospital stay, and the overall survival was also significantly prolonged in patients with residual tumor after palliative resection compared to unresected patients palliated with double-bypass (Figure 1) (12, 17). However, it should be emphasized that successful palliative surgery depends on the ability of the institution to provide a safe operation with minimal peri-operative morbidity and mortality.

A recent series (30) included 240 patients with a pancreatic head tumor who underwent laparotomy to assess tumor resectability. In 44 patients, the tumor was not resected because of distant metastases (n=20), major vascular involvement or local tumor infiltration (n=24), not detected during the pre-operative workup. A palliative biliary and gastric bypass was performed in these patients. All other patients underwent a subtotal (Whipple’s resection, n=164) or total (n=32) pancreaticoduodenectomy. In 56 cases after Whipple’s resection, microscopic tumor invasion was found at the resection margins and these resections were, therefore, considered as palliative. The hospital mortality, morbidity and the long-term survival of patients who had undergone a biliary and gastric bypass for locally advanced tumor were compared with those of a matched group of patients who had undergone a macroscopically radical Whipple’s resection which, on microscopic examination, proved to be non-radical. Post-operative complications (intra-abdominal abscess, gastrointestinal hemorrhage, anastomotic leakage, delayed gastric emptying) did not differ significantly between the groups. The hospital mortality was 0% and 3% in the bypass- and palliative-resected groups, respectively.

Klempnauer et al. (26) reported on 23 liver resections performed in 22 patients due to hepatic metastases of pancreatic (n=20) or ampullary (n=2) carcinomas, from 1971 to 1995. In 16 patients, the solitary hepatic lesions were removed synchronously with the pancreatic primary tumor. In 7 cases a liver resection was performed for metachronous metastases. The peri-operative mortality was 4.3%. Curative R0-resection was accomplished in 69% of the patients with synchronous, and in 100% with metachronous, liver metastases. The median survival time was 8.3 months after synchronous and 5.8 months after metachronous hepatic resection. The 1-year survivals were 41 and 40%, respectively. The authors concluded that, although distant metastases are a definite sign of progressed tumor stage, the prognosis of patients with hepatic metastases should not be considered hopeless. In view of a comparatively small operative risk, there is a chance for individual patients to gain valuable survival time.

**Palliative Chemotherapy**

Single agent Gemcitabine remains the standard of care in 2005 for the treatment of patients with advanced pancreatic cancer. The addition of Cisplatin or Oxaliplatin to Gemcitabine has been shown to increase the response rate...
and progression-free survival, when compared to Gemcitabine alone in phase III studies. However, there was no significant improvement in overall survival, and the addition of these agents to Gemcitabine cannot be routinely recommended (1).

Conclusion

Pancreatic cancer remains a disease with a poor prognosis, even after surgery with curative intent. Despite this, surgical resection offers the only possibility of a long-term cure. In high-volume centers, the morbidity and mortality associated with pancreatic surgery have declined significantly in the past two decades. Even resection of the SMV or portal vein can be performed safely and offer a pattern of recurrence and survival comparable to the standard R0 Whipple procedure. The presence of tumor invasion into the SMA or the celiac trunk remains a contraindication for pancreaticoduodenectomy. In high-volume centers it should be justified to perform a palliative pancreaticoduodenectomy in highly selected patients, but this awaits further evaluation in randomized trials. Although it is controversial, adjuvant/palliative CT or chemoradiotherapy should follow surgical intervention.

References


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