Surgical Advances in Pancreatic Cancer
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Introduction

Despite improvements in diagnosis and therapy, pancreatic cancer is still a devastating disease, which is presently the fourth leading cause of cancer related deaths in Western countries.\textsuperscript{1} Although significant efforts have been made, only little progress has been achieved in the last decades with respect to the overall survival of pancreatic cancer patients. It is still a challenging task to diagnose pancreatic cancer at an early stage that offers the chance of successful therapy. Thus, the overall resectability rate of pancreatic cancer is only 10 to 15\%.\textsuperscript{2} Rapid tumor progression, and a striking resistance to chemotherapy, radiotherapy, and targeted/biological therapies\textsuperscript{3, 4} contribute to the poor prognosis. These facts together result in low tumor resectability rates after diagnosis, early tumor recurrence after resection, and poor overall survival rates. Even after potential curative resection, long term survival is not satisfactory with around 20\%, but subgroup analyses of e.g. lymph node negative tumors that have been resected with negative margins demonstrate 5-year survival rates of about 40\%.\textsuperscript{5} In the last decade the surgical outcome has improved, mostly because of improving perioperative treatment. Birkmeyer et al.\textsuperscript{6} demonstrated that operation related morbidity and mortality significantly decreases in centers with high patient load. This critical aspect of the value of centralization on the outcome of pancreatic surgery in “high volume institutions,” has been demonstrated in numerous studies.\textsuperscript{7} The current mortality rate following pancreatic resection is well below 5\%\textsuperscript{8} in specialized surgical centers. Improvements in multimodal therapy\textsuperscript{9} combined with more experienced surgical treatment of pancreatic cancer at high volume centers have improved the long-term survival as well as the quality of life of pancreatic cancer patients.
Operations for tumors of the head of the pancreas

Periampullary cancers account for about 5% of all gastrointestinal tract malignancies,\textsuperscript{10} which can be divided into four groups of tumor entities: (i) periampullary tumors that originate from the pancreas (pancreatic cancer), (ii) the mucosa of the ampulla of Vateri (ampullary carcinoma), (iii) the common distal bile duct (distal cholangiocellular carcinoma) or (iv) the mucosa of the duodenum (duodenal adenocarcinoma). The most common periampullary malignancy is pancreatic cancer, accounting for 3% of all gastrointestinal tumors. Carcinoma of the ampulla of Vateri is the second most common periampullary malignancy.\textsuperscript{11} Distal cholangiocellular carcinoma is less frequent and duodenal adenocarcinoma of the periampullary region is only rarely seen.\textsuperscript{12} The relatively poor prognosis for periampullary carcinomas, excluding pancreatic head cancers, with five-year survival rates varying between 24 and 50%, still remains a challenge.\textsuperscript{12}

One limitation for studies reporting on periampullary carcinomas, excluding pancreatic cancer is that these studies contain only relatively small numbers of study subjects.\textsuperscript{11-13} Nevertheless, the standard therapy of choice for all entities of periampullary carcinomas is a partial pancreatoduodenectomy (PD), irrespective of the underlying histology.\textsuperscript{12} Despite their low incidence rates, ampullary, cholangiocellular, and duodenal cancers are attracting attention due to their suspected diverse biological behavior leading to improved survival rates in comparison to pancreatic cancer.\textsuperscript{10, 12} In the next passages of this chapter, we will focus on the therapy modalities for pancreatic cancer.

The majority of all pancreatic cancers (approximately 60%) arise in the head of the pancreas. In these cases a partial pancreatoduodenectomy (classical Kausch-Whipple procedure) or a pylorus preserving pancreatoduodenectomy is considered the gold standard for surgical therapy. Cameron et al.\textsuperscript{5} demonstrated in a retrospective review of 1000 pancreaticoduodenectomies- performed by a single surgeon- the management and outcome of these patients. The evolution of this operative procedure was also analyzed over 5 decades, demonstrating a significant drop in median operative time and in the postoperative hospital stay from initially 17 to 9 days. The mortality rate in this series was 1%. The overall 5-year survival rate was 18%, for the lymph-node negative patients it increased to 32% and for lymph-node negative patients with negative resection margins it reached 41%.\textsuperscript{5} This study demonstrates on the basis of a large patient
population, how the improvements in surgery as well as advances in peri and postoperative care can increase the long term survival rates of patients with pancreatic cancer treated by pancreateoduodenectomy. This operation has become safe and effective, with low hospital mortality rates. The question which type of the pancreateoduodenectomy suits best has been controversially discussed. However, several randomized controlled studies have been performed, comparing the classical Kausch-Whipple with the pylorus-preserving pancreateoduodenectomy.

**Classical Kausch-Whipple vs. pylorus preserving pancreateoduodenectomy (PD)**

The classical procedure for operating on pancreatic head masses was the Kausch-Whipple operation that consists of the resection of the pancreatic head, the duodenum along with a distal gastrectomy, cholecystectomy, removal of the distal common bile duct segment, proximal jejunum, and en-bloc resection of regional lymph nodes. With the re-introduction of the pylorus-preserving pancreaticoduodenectomy, a modified procedure without resection of the pylorus and the distal part of the stomach, a controversial debate on what should be the standard pancreatic head resection had started early. Initial studies reported a higher incidence of complications, such as delayed gastric emptying and concerns about less oncological effectiveness of the pylorus-preserving procedure. Meanwhile, randomized controlled trials as well as a meta-analysis have demonstrated that both perioperative morbidity and long-term outcome are equal for the classical Kausch-Whipple and the pylorus preserving PD. Even though the question which procedure should be performed for pancreatic head cancer is not definitively answered, both procedures can be recommended for resection of cancer arising in the head of the pancreas, according to the most recent available data.

**Distal pancreatectomy**

Tumors that arise in the body or tail of the pancreas can be operated with a distal pancreatectomy. The distal pancreatectomy consists of the removal of the portion of the pancreas extending to the left of the midline but does not include resection of the duodenum and the distal bile duct. The advantage of this procedure, compared to the PD procedure, is that a pancreatic anastomosis is not needed in most cases. Therefore the distal pancreatectomy has been considered as a simpler surgical procedure in
comparison to a pancreaticoduodenectomy. However, pancreatic fistulas occur in 10-20% of cases and result in increased postoperative morbidity, length of hospital stay, and overall costs.\textsuperscript{17} In a recent retrospective study, stapler closure of the pancreatic remnant has been reported to be associated with significantly higher fistula rates.\textsuperscript{18} Therefore, randomized controlled trials have been initiated to identify the best technique for closure of the pancreatic stump.

Another important aspect of distal pancreatectomy is the often concomitantly performed splenectomy. Schwarz et al.\textsuperscript{19} showed that the median survival of patients undergoing distal pancreatectomy with curative intention for pancreatic cancer was 17.8 months without splenectomy and 12.2 months with splenectomy. The en-bloc resection the spleen was believed to be necessary due to regional lymph nodes and the close relation of the splenic artery and vein to the body of the pancreas. Hence, splenic preservation was thought to compromise the oncological resection. Schwarz et al. recommended therefore that the spleen should be preserved unless the splenic capsule was directly involved, or nodal clearance required a splenectomy.\textsuperscript{19}

**Total pancreatectomy**

In order to improve postoperative outcome, the radical total pancreatectomy has been introduced to the treatment of pancreatic head cancer. Obviously, this more radical approach with resecting the whole gland would include the elimination of multifocal disease and complications emanating from the pancreatic remnant (e.g. pancreatic fistula). Furthermore, the additional resection of the body and tail of the pancreas would increase the possibilities for a more extensive lymphadenectomy around the body and tail of the pancreas as well as tumor resection adjacent to the retroperitoneum. However, recent studies revealed that the occurrence of multicentric pancreatic cancer is fairly uncommon, occurring in less than 10% of cases.\textsuperscript{20} Moreover, randomized trials on extended lymphadenectomy showed no significant oncological benefits, especially because lymph nodes around the body and tail of the gland are rarely involved with metastatic disease from pancreatic head cancer. In contrast, the removal of the entire pancreas results in severe endocrine and exocrine insufficiency. In terms of studies, Muller et al.\textsuperscript{21} reported that total pancreatectomy had a surgical morbidity of 24% and an overall mortality rate of 4.8%. The global health status of patients, that have undergone a total pancreatectomy was after 23 months comparable to that of pylorus preserving
pancreatoduodenectomies, although quality of life (QoL) was reduced. They concluded, that total pancreatectomy can be a treatment option for selected patients.\textsuperscript{21} In conclusion, total pancreatectomy should not be performed routinely for pancreatic head cancer. Rare exceptions may include tumor extension to the body/ tail of the pancreas and the presence of an atrophic, soft and friable pancreatic parenchyma for which an anastomosis is not considered safe.

**Venous resection**

The specific anatomic position in close proximity to the portal vein, the celiac trunk, superior mesenteric vessels, combined with the extensive and aggressive growth behavior predisposes pancreatic carcinoma to affect or even infiltrate these structures. Therefore venous resections were suggested in order to obtain complete tumor resections and avoid R1 or even R2 resections. Recent studies indicate that venous resections can be performed without increased morbidity and mortality.\textsuperscript{22} However, data on long-term survival after venous resection are less clear. A recent systematic review on portal vein resection reported a median survival of only 13 months following resection. In this study patients were treated from 1965 to 2003 and positive resection margins occurred in about 40\% of cases.\textsuperscript{23} Better survival rates have been demonstrated in some single center studies.\textsuperscript{22} Irrespectively, numerous studies have shown that partial resection of the portal vein/superior mesenteric vein can be carried out safely, without the risk of increased morbidity/mortality. In addition, a randomized multicenter trial comparing resection and radiochemotherapy for locally resectable invasive pancreatic cancer reported a median survival of >17 months in the surgically treated group versus 11 months in the radiochemotherapy arm.\textsuperscript{24} These studies together demonstrate that venous infiltration should not be considered a contraindication for resection in pancreatic cancer if a potential curative resection can be achieved. This strategy has also been adopted in current guidelines in the USA as well as in Europe.

**Extended lymphadenectomy**

Attempts have been made to decrease the high local recurrence rate following pancreatic cancer resection by performing a more radical lymph-node dissection. The rationale for this approach was the observation of affected lymph nodes in the paraaortic
region encapsulated between the celiac trunk and the origin of the superior mesenteric artery. Therefore, the idea to radically operate and remove all these lymph-nodes seemed to be an appropriate approach. Indeed, initial retrospective studies on extended radical lymphadenectomy in cancer of the pancreatic head reported a survival benefit in comparison to standard resection. However randomized controlled trials revealed different result. In fact, overall morbidity with diarrhea and delayed gastric emptying tended to occur more frequently after extended lymphadenectomy. A study by Yeo et al. demonstrated comparable mortality and survival rates, whereas morbidity was significantly increased in the extended lymphadenectomy group with increased rates of postoperative diarrhea and resulting malnutrition. This study failed to report differences in 1, 3, and 5-year survival rates. A meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer including three of four randomized controlled trials confirmed the data from Yeo et al. and Farnell et al. indicating no significant differences between the standard and extended procedure. There were no differences in morbidity and mortality rates, with a trend towards higher incidence of delayed gastric emptying for extended lymphadenectomy. Although the available randomized studies are underpowered and lack clinical standardization regarding the extent of lymphadenectomy, adequate randomized controlled trials that would be needed to determine any potential survival benefit, are highly impractical. Therefore, extended radical lymphadenectomy should not be performed routinely.

**Does R1 resection limits surgical practice?**

A key factor for long-term survival of patients with resected pancreatic cancer is a complete tumor resection with negative resection margins (R0 resection). Although R0 resection rates have been reported in up to 75% in large surgical series, most patients develop local and/or distant recurrences which could be caused by microscopic residual disease (R1 resection) at the time of resection. Using new standardized pathological processing techniques and protocols, a recent study by Esposito et al. displayed R1 resection rates for pancreatic cancer of up to 76%. The most common anatomical site for evidence of tumor remnants was the posterior margin. In contrast, the R1 resection rate was 14% (carried out by the same team of surgeons) when no standardized protocol was used. These results demonstrate the particular need of a thorough and standardized pathological examination of pancreatic cancer specimen, in order to allow
a precise investigation and definition of prognostic relevant histopathological markers. Furthermore, these data finally influence the decision making with respect to therapeutic options such as adjuvant therapy.

**Conclusion**

In the last decades major pancreatic operations have evolved into safe and standard surgical procedures. Most progress has been made in peri and postoperative practices and treatment modalities. Therefore, in high-volume centers, surgery for pancreatic cancer is safe with morbidity and mortality rates that are not different from other major gastrointestinal surgeries. The 5-year survival has increased to 15%-25% following resection of pancreatic cancer. However, the notable breakthrough has not yet come and the overall prognosis of pancreatic cancer has barely changed over the years. Future studies and potentially multimodal therapies are being established in order to improve long-term survival of pancreatic cancer patients. Adjuvant chemotherapy with either 5-FU or gemcitabine has been shown to improve prognosis in resectable pancreatic cancer. Combinations of chemoradiation and interferon-\(\alpha\) as well as novel biological therapies present promising future perspectives in the treatment of pancreatic cancer. Extensive surgery should be critically evaluated, extensive/radical lymphadenectomy has not shown to improve prognosis; however, an isolated portal vein involvement on the other hand does not represent a contraindication for tumor resection. More extensive surgery on metastatic\(^{31}\) and recurrent disease\(^{32}\) remains questionable, although some studies seem promising.
References:


