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TOPIC HIGHLIGHT

Michiko Yamagata, MD, PhD, *Series Editor*

Recent advances and limitations of surgical treatment for pancreatic cancer

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Abstract

Recent advances in surgical treatment for pancreatic cancer have been remarkable. Pancreatoduodenectomy is a standard surgical procedure for cancer of the pancreatic head, and is now indicated even for elderly patients over 80 years of age. Pancreatoduodenectomy with combined resection of the peripancreatic vessels has improved survival, but extended resection including lymph nodes is considered to have no extra survival benefit. Furthermore, laparoscopic resection procedures including pancreatoduodenectomy, distal pancreatectomy, enucleation and central pancreatectomy can now be performed safely. Neoadjuvant or adjuvant chemotherapy using gemcitabine may further improve the surgical outcome. An understanding of the oncological aspects of pancreatic cancer and the development of surgical techniques and chemotherapy may further contribute to improving the outcome of surgery for pancreatic cancer.

Key words: Chemotherapy; Laparoscopic surgery; Pancreatic cancer; Pancreatoduodenectomy; Pancreatic fistula

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INTRODUCTION

Although curative surgical resection is the best treatment for pancreatic cancer, morbidity and mortality after surgery are still high and prognosis is still unsatisfactory. Pancreatic cancer requires pancreatoduodenectomy (PD) or distal pancreatectomy. Advanced cancers may invade the portal vein and nerve plexus, and subsequently these structures may also need to be resected[1,2]. Recent advances in preoperative management and surgical techniques have facilitated safe and successful resection of such cancers. Herein, the recent advances and limitations of surgical treatment for pancreatic cancer are reviewed.

PREOPERATIVE BILIARY DRAINAGE

It has not been clarified whether PD or major hepatectomy should be performed without preoperative biliary drainage (PBD) in patients with jaundice. Although PBD is considered to improve liver function, the benefits of the procedure are controversial. Van der Gaag *et al*[3] performed a multicenter, randomized trial involving 202 patients with jaundice due to cancer of the pancreatic head (96 undergoing early surgery with no drainage and 106 undergoing PBD). The rates of serious complications were 39% in the early-surgery group without drainage and 74% in the PBD group. Surgery-related complications occurred in 35 patients in the early-surgery group and in 48 patients in the PBD group. Mortality and the length of hospital stay did not differ significantly between the groups. They concluded that routine PBD in patients

undergoing surgery for cancer of the pancreatic head increases the rate of complications. Furthermore, Mezhir *et al*[4] analyzed the complications related to PBD in patients with cancer of the pancreatic head and concluded that PBD increased the incidence of infectious complications including wound infection and intra-abdominal abscess, although the incidence of anastomotic leakage was unaffected. On this basis they considered that routine use of PBD remains unjustified.

SURGICAL TREATMENT

Although surgical treatment for pancreatic cancer is usually indicated for patients younger than 80 years, the postoperative results for patients older than 80 years still remain unclear. Tani *et al*[5] found that the incidence of delayed gastric emptying in such elderly patients was higher, although not to a significant degree. The other outcomes in the elderly group were similar to those of patients younger than 80 years of age. They concluded that PD was a feasible surgical procedure for elderly patients who had a good performance status.

Pancreatic ductal adenocarcinoma is an aggressive disease. Surgical resection with negative margins (R0) offers the only opportunity for cure. Patients who have advanced disease that limits the chance for R0 surgical resection may undergo margin positive PD. Lavu *et al*[6] reported that median survival was 27.2 mo for R0, 15.6 mo for margin-positive PD, 6.5 mo for palliative bypass and 5.4 mo for celiac plexus neurolysis alone. They concluded that margin-positive PD in highly selected patients can be performed safely, with low perioperative morbidity and mortality, and is superior to palliative bypass for locally advanced pancreatic ductal adenocarcinoma. Furthermore, Hüser *et al*[7] recommended that prophylactic gastroenterostomy should be performed during surgical exploration of patients with unresectable pancreatic head tumors because it reduces the incidence of long-term gastroduodenal obstruction without impairing short-term outcome.

The characteristics of pancreas cancer include invasion to the superior mesenteric vein or nerve plexus, and lymph node metastasis. Boggi *et al*[2] evaluated the operative risk and prognostic implications of pancreatectomy plus resection and reconstruction of peripancreatic vessels in patients with pancreatic adenocarcinoma. They found that pancreatectomy plus resection and reconstruction of peripancreatic vessels could be performed as safely as palliation or conventional pancreatectomy, and was associated with better survival when compared to palliation. Makino *et al*[1] investigated the patterns of nerve plexus invasion. Extrapancreatic nerve plexus invasion by carcinoma of the pancreatic head could be divided into two patterns based on the embryological structure of the pancreas and the location of the tumor. Patients with carcinoma in the ventral pancreas frequently had pancreatic head plexus 1, pancreatic head plexus 2, and superior mesenteric arterial plexus invasion. Patients with carcinoma in the dorsal pancreas had invasion into the common hepatic artery plexus and the plexus within the hepatoduodenal ligament. They considered that this information could be useful for determining the surgical strategy for carcinoma of the pancreas head. Hernandez *et al*[8] evaluated the survival benefit of extending resections to obtain microscopically negative margins after intraoperative frozen sections had revealed cancer positivity, but found that this approach did not improve survival.

Recently, visceral ischemic complications have attracted the attention of surgeons[9]. Ischemic complications are an underestimated cause of death after PD, and are due to pre-existing stenosis of the celiac axis and superior mesenteric artery, or intraoperative hepatic artery injury. Pre-existing arterial stenosis can be detected by routine multi-detector CT. Preoperative endovascular stenting for intrinsic stenosis, division of the median arcuate ligament for extrinsic compression, and meticulous dissection of the hepatic artery can help to minimize ischemic complications.

Pancreatic fistula is one of the most common complications after PD. Berger *et al*[10] investigated the utility of duct-to-mucosa pancreatojejunostomy in a randomized, prospective, dual-institutional trial and found considerably fewer fistulas with invagination compared with duct-to-mucosa anastomosis after PD. Higher incidence rates of pancreatic fistula were confirmed in patients with soft pancreas than in those with hard pancreas.

Laparoscopic resection

The role of laparoscopy in pancreatic surgery was originally relegated to staging and palliation for pancreatic surgery. Laparoscopic staging of pancreas tumors was shown to be superior to dynamic CT for visualizing small, occult liver and peritoneal metastases and was useful for avoidance of unnecessary laparotomy in patients with unresectable disease[11,12]. The addition of laparoscopic ultrasound during laparoscopic staging enhanced the ability of laparoscopy to determine tumor resectability with an accuracy approaching that of open exploration without any significant increase in morbidity or mortality. Gagner and Pomp were the first to report a successful laparoscopic pancreatic resection in 1994[13]. Two years later, Sussman and colleagues published the first report of a laparoscopic distal pancreatectomy for insulinoma[14]. Currently, five operative procedures are commonly performed on the pancreas for neoplastic disease: diagnostic laparoscopy with or without biopsy, PD, tumor enucleation, central pancreatectomy and distal pancreatectomy with or without splenectomy[15]. These laparoscopic procedures are particularly recommended for benign tumors, but it is very difficult to make clear recommendations with regard to laparoscopic resection of malignant pancreatic tumors due to a lack of conclusive data.

Radiofrequency ablation

Girelli *et al*[16] employed radiofrequency ablation for locally advanced pancreatic cancer. The 30-d mortality rate was 2%, and abdominal complications occurred in 24% of patients, being associated with the procedure in half of such cases. They concluded that radiofrequency abla-

tion of locally advanced pancreatic cancer is feasible and relatively well tolerated.

Chemotherapy

Heinrich *et al*[17] investigated the clinical utility of neoadjuvant chemotherapy using gemcitabine and cisplatin. The surgical morbidity was low without perioperative death, and one pancreatic fistula occurred. A histologic response was documented in 54% of patients, and cytopathic effects in 83%. Neoadjuvant chemotherapy elicited a significant metabolic and histologic response, which was best predicted by PET. Most importantly, surgery after neoadjuvant chemotherapy was shown to be safe. Furthermore, Ohigashi *et al*[18] evaluated the feasibility and efficacy of preoperative full-dose gemcitabine, concurrent 3D-conformal radiation, surgery and postoperative liver perfusion chemotherapy for T3 pancreatic cancer. They were able to effectively reduce the incidence of both local and liver recurrence, possibly contributing to improving the long-term outcome. Pancreatic resection combined with neoadjuvant or adjuvant chemotherapy undoubtedly contributes to improvement in outcome.

PROGNOSIS

The prognosis of pancreatic ductal adenocarcinoma is dismal, and influenced by tumor stage. Massucco *et al*[19] analyzed the prognostic significance of variables related to nodal involvement (node status, number of disease-positive nodes, node ratio and site of nodal metastases) in patients with resected pancreatic head cancer. They found that the level of nodal metastatic spread was a statistically significant prognostic factor, and that both the number of disease-positive nodes and the node ratio were an accurate proxy for node level (1: peri-pancreatic nodes, 2: nodes along the main arteries and hepatic hilum, 3: pre-aortic nodes), perhaps contributing to patient risk stratification.

Obesity is reported to influence cancer-related outcome. Fleming *et al*[20] considered that obese patients with a body mass index (BMI) of more than 35 were more likely to have node-positive pancreatic cancer and to show shorter survival after surgical resection. Data suggest that the negative influence of a BMI exceeding 35 on the incidence of lymph node metastasis and disease-free and overall survival is unrelated to the potential complexity of performing major oncologic surgery in obese patients. In fact, it has been shown that increased pancreatic fat promotes dissemination and lethality of pancreatic cancer. Pancreatic steatosis is considered to alter the tumor microenvironment, enhance tumor spread and contribute to the early demise of patients with pancreatic adenocarcinoma[21,22].

Readmission after PD is not uncommon. One report has indicated that 59% of patients were readmitted within 1 year following PD and that 47% were readmitted to a secondary hospital. Readmission was associated with poorer median survival in comparison to patients who were not readmitted (10.5 *vs* 22 mo)[23].

Long-term survival after pancreatectomy for pancreatic duct adenocarcinoma has been rarely reported. Adam *et al*[24] reported a French multicenter series of long-term survivors (>5 years) comprising 20 men and 10 women. Three patients underwent portal vein resection, 1 underwent hepatic artery resection-reconstruction, and 1 underwent segmentectomy for liver metastasis. However, all the resections were complete, both macroscopically and microscopically (R0). They concluded that pancreatic duct adenocarcinoma can be cured, and that long-term survival after R0 curative surgery has become a reality. These long-term survivors did not fulfill the ideal prognostic criteria, and some even presented with advanced disease.

CONCLUSION

Although pancreatic cancer is still associated with poor prognosis, an understanding of the oncological aspects of pancreatic cancer and the development of surgical techniques, including laparoscopic surgery, and chemotherapy may further contribute to improving the outcome of surgery for pancreatic cancer.

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