Benign Tumors of the Pancreas—Radical Surgery Versus Parenchyma-Sparing Local Resection—the Challenge Facing Surgeons

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Abstract

Pancreaticoduodenectomy and left-sided pancreatectomy are the surgical treatment standards for tumors of the pancreas. Surgeons, who are requested to treat patients with benign tumors, using standard oncological resections, face the challenge of sacrificing pancreatic and extra-pancreatic tissue. Tumor enucleation, pancreatic middle segment resection and local, duodenum-preserving pancreatic head resections are surgical procedures increasingly used as alternative treatment modalities compared to classical pancreatic resections. Use of local resection procedures for cystic neoplasms and neuro-endocrine tumors of the pancreas (panNETs) is associated with an improvement of procedure-related morbidity, when compared to classical Whipple OP (PD) and left-sided pancreatectomy (LP). The procedure-related advantages are a 90-day mortality below 1% and a low level of POPF B+C rates. Most importantly, the long-term benefits of the use of local surgical procedures are the preservation of the endocrine and exocrine pancreatic functions. PD performed for benign tumors on preoperative normo-glycemic patients is followed by the postoperative development of new onset of diabetes mellitus (NODM) in 4 to 24% of patients, measured by fasting blood glucose and/or oral/intravenous glucose tolerance test, according to the criteria of the international consensus guidelines. Persistence of new diabetes mellitus during the long-term follow-up after PD for benign tumors is observed in 14.5% of cases and after surgery for malignant tumors in 15.5%. Pancreatic exocrine insufficiency after PD is found in the long-term follow-up for benign tumors in 25% and for malignant tumors in 49%. Following LP, 14–31% of patients experience postoperatively NODM; many of the patients subsequently change to insulin-dependent diabetes mellitus (IDDM). The decision-making for cystic neoplasms and panNETs of the pancreas should be guided by the low surgical risk and the preservation of pancreatic metabolic functions when undergoing a limited, local, tissue-sparing procedure.

Keywords Benign tumors of the pancreas · Parenchyma-sparing resections · Radical surgery · Local tumor extirpation · Cystic neoplasms · Neuroendocrine tumors

Pancreaticoduodenectomy (PD) and left-sided pancreatectomy (LP) are highly developed surgical treatment procedures for malignant and benign pancreatic tumors.^{1,2} PD is the standard treatment for pancreatic head and periampullary cancers. Surgery-related postoperative complications are significantly reduced after PD following standardization of the procedure and the application of evidence-based surgical techniques.

High levels of intensive care treatment and interventional management for local complications have additionally led to a considerable reduction of overall and surgery-related morbidity. The in-hospital mortality following a PD has fallen to 0–3% in specialized high-volume centers,^{3–5} while large multi-institutional reports indicate hospital mortality of 3–7%.^{6–9}

Following left-sided pancreatectomy—with and without splenectomy—studies performed over the previous 10 years have reported severe, surgery-related morbidity of < 15% and an in-hospital mortality of 0.6–2%^{9–11}; hospital mortality was 3.5% after LP reported in a multi-institutional study covering data of 7872 patients investigated between 1998 and 2003.⁹ In LP for pancreatic neuro-endocrine tumors (panNETs), a systematic review based on the results of 267 patients revealed a post-operative pancreatic fistula (POPF) B + C rate of 14% and an in-hospital mortality of 4%.¹² LP, when performed

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laparoscopically, is, according to the results of two meta-analyses covering data of 4360 patients, associated with a significant reduction of overall early postoperative morbidity, a lower rate of pancreatic fistula B + C, a shorter hospitalization time and a higher rate of spleen preservation when compared to open LP. However, open LP is likely to be performed for patients with ductal pancreatic adenocarcinoma (DPAC), while laparoscopic LP is performed more frequently for benign tumors.^{13,14} A further improvement has been reported when applying robot-assisted LP in terms of lesser intra-operative blood loss, better preservation of splenic vessels, lower conversion rate, and a shorter time for surgery, compared to laparoscopic LP.¹⁵

The progress in early postoperative outcomes after PD and LP has consequently led to an extension of the use for benign and premalignant neoplasms. Moreover, based on substantial data, surgical treatment is extended to small benign cystic neoplasms (< 3 cm)¹⁶ and neuro-endocrine tumors of < 1.5–2 cm,¹⁷ to reduce the risk of developing cancer during observational care.

However, long-term metabolic consequences of PD and LP applied for benign pancreatic tumors remain unaddressed. The frequency of diabetes mellitus (DM), impaired glucose tolerance and exocrine pancreatic dysfunctions after PD and LP come into question, when these procedures are performed on patients diagnosed with benign neoplasms leading to cure and thus long-term survival. PD is associated with a loss of tissue from the pancreas, stomach, duodenum and biliary tree, leading to a significant decrease of endocrine and exocrine pancreatic functions and to reduced functional capacity of the entero-insular regulatory pathways. Recently, published data of a systematic review and meta-analysis involving 1295 patients revealed the frequency, degree and long-term persistence of endocrine and exocrine dysfunctions after PD.¹⁸ PD performed on preoperative normoglycemic patients for benign tumors was followed by postoperative development of new onset of diabetes (NODM) in 4–24% of patients.^{19–21} Patients with preoperative DM displayed, following PD, an impaired glucose tolerance and escalation of DM in 40–50%, half of cases progressed to a stage of insulin-dependent diabetes.¹⁸ Patients suffering PDAC and pre-existing short-term diabetes, when undergoing PD experience a resolution of DM in 20–40% of cases in the early postoperative period. However, persistence of NODM during the long-term follow-up after PD for benign tumors up to 8 years was observed in 14.5% of cases, and after surgery for malignant tumors in 15.5% of patients.¹⁸

Pancreatic exocrine insufficiency after PD is found during the early postoperative months in 23–80% of patients. Exocrine insufficiency with the need for enzyme supplementation was found in the long-term follow-up after PD for benign tumors in 25.2% and for malignant tumors in 49.1% of patients.¹⁸

Following left-sided pancreatic resection, 14–31% of patients are observed to develop NODM; many of the patients subsequently developed IDDM.^{22–24} Following pancreatic left resection corresponding to a volume of the pancreatic specimen

of < 25, 25–50, and > 50% of the pancreas for benign and malignant tumors, patients displayed impaired endocrine functions a year after surgery in 34.3%, 53.3%, and 73.3% of cases, respectively.²³ Data derived from metabolic investigations of organ donors of the left pancreas confirm the endocrine and exocrine dysfunctions occurring after LP. Healthy humans, who underwent hemi-pancreatectomy for organ donation, developed during the long-term follow-up in 46% persisting impaired glucose tolerance or diabetes.²⁴ Among 28 living pancreas donors, 25% displayed abnormal glucose tolerance and impaired insulin secretion following oral glucose tolerance (OGT) testing a year after donation of the left pancreas.²⁵

Prevalence of benign tumors of the pancreas varies presently with increasing numbers between 5 and 15% reported from surgical institutions. Among pancreatic neoplasms, intraductal papillary mucinous neoplasms (IPMNs) are the predominant cystic tumors. IPMNs are observed predominantly in the pancreatic head, particularly in males of older age. Mucinous cystic neoplasms (MCNs) are located in 80% of cases in the body and tail and in 15% in the pancreatic head, 85% found in middle-aged female patients.^{26,27} Serous pseudo-papillary neoplasms (SPNs) develop more frequently in female patients aged 40 to 50 years and are equally distributed throughout the pancreas.

IPMN, MCN, and SPN are associated with a considerable risk of malignancy. Symptomatic patients, diagnosed with a cystic neoplasm of the pancreas should consequently undergo surgical treatment. Incidentally detected tumorous lesions of the pancreas without tumor-related symptoms are found in up to 50% of patients who undergo abdominal diagnostics. A majority of lesions are found to be benign at the time of initial presentation.²⁸ However, correct prediction of the nature and biology of pancreatic neoplasms remains a difficult task because of an incomplete understanding of the nature of the diseases.^{29–34} The presence of high-grade dysplasia associated with IPMNs and MCNs are criteria that warrant a change from surveillance to definite surgical management. To maintain the risk of undertreatment or late surgical management as low as possible, early resection of cystic neoplasms sized < 3 cm is recommended.^{16,35,36}

Among the group of panNETs, a majority develops sporadically. Up to 90% of panNETs are classified as non-functional tumors (nf-panNETs). PanNETs are predominantly located in the pancreatic head and tail. Most patients are aged below 55 years, when the tumor is detected. All panNETs are considered potentially malignant.^{37,38} Non-functional, asymptomatic panNETs of < 2 cm are an increasing subgroup posing a challenging risk assessment for the detection of malignancy and consequently for selecting an appropriate management protocol.

Furthermore, there is a substantial and increasing body of data that surgical management of patients with benign nf-panNETs is associated with significantly better overall survival at 1, 3, and 5 years compared to observational management,^{17,39} extending the indication to surgical treatment of patients with panNETs of < 2 cm of size.

Surgeons, who are requested to treat patients with benign tumors using standard oncological resections, face the challenge of unnecessarily sacrificing pancreatic and extra-pancreatic tissue. Parenchyma-sparing surgical procedures are increasingly used as alternative surgical treatment modalities compared to classical resection techniques. The first local, parenchyma-sparing resection of a periampullary tumor performed William S. Halsted at John Hopkins University Hospital in 1889, whereby he successfully resected a papillary tumor by ampullectomy; the tumor in a papillary diverticulum became finally a cancerous lesion of the papilla of Vater.⁴⁰

Tumor enucleation (EN), pancreatic middle segment resection (PMSR) and duodenum-preserving partial and total pancreatic head resection (DPPHR) are the limited surgical procedures, associated with pancreatic and extra-pancreatic tissue conservation. Although presently not established as standard surgical procedures, the local, parenchyma-sparing resection strategies used for the management of benign neoplasms have the potentials to lower significantly early-postoperative morbidity rates, yielding a very low hospital mortality, when compared to standard procedures. The most important advantage of the limited, parenchyma-sparing surgical techniques is their ability to preserve pancreatic endocrine and exocrine functions to avoid NODM and pancreatic exocrine dysfunctions in almost all of the patients in the long-term outcome.

Enucleation (EN) is increasingly performed for benign pancreatic tumors and is most frequently applied for panNETs. A recently published meta-analysis disclosed for EN a frequency of pancreatic fistula of 25.5%, fistula grades B and C < 15%; severe early postoperative complications were < 10%. Time for surgery, intraoperative blood loss and length of hospital stay were significantly lower after EN, when compared to pancreatic left resection.⁴¹ Two systematic reviews involving 838 and 624 patients, respectively, demonstrated a hospital mortality after EN of 0.9 and 3.0% respectively.^{12,41} A tumor size of > 3 cm is considered to be borderline for EN, because tumor abutment to the main pancreatic duct increases the risk of duct lesion and POPF grade B/C, which are the dominant postoperative local complications after EN.⁴²

Middle segment resection of the pancreas is a demanding procedure for benign tumors, because of the need to manage two resection surfaces of the pancreas. Based on a systematic review, PMSR was associated with a pancreatic fistula rate of 51%, a POPF grade B + C of 17%, a reintervention rate of 7%, and a hospital mortality of 0%. Furthermore, PMSR was associated with a 16% rate of rehospitalization of patients.^{43,44} Pancreatic fistula grades B + C and postoperative hemorrhage are the most important surgery-related complications observed after PMSR.

DPPHR is predominantly performed for inflammatory tumors of the pancreatic head. Cystic neoplasms located in the pancreatic head and uncinate process are treated in high-volume centers by applying duodenum-preserving techniques. Duodenum-

preserving total pancreatic head resection involves the same surgical steps as performed in PD, except dissection of the duodenum from the pancreatic head towards the papilla, avoiding peripapillary ischemia of the duodenum.^{45,46} Among 416 patients evaluated in a meta-analysis after DPPHR for benign and low-risk neoplasms, severe, early surgery-related complications were reported in 11% of patients, with a reoperation frequency of 2%; 90-day hospital mortality was < 0.5% and rehospitalization 3.0%.⁴⁷ Assessment of the endocrine and exocrine pancreatic functions after DPPHR for benign neoplasms compared to PD indicated that DPPHR preserves the endocrine and exocrine pancreatic functions, while PD was associated with a significant increase in the incidence and persistence of NODM and with a considerable pancreatic exocrine insufficiency, observed in the long-term outcome.⁴⁶ Endocrine and exocrine pancreatic dysfunctions after DPPHR were assessed in 4 and 9% of the patients, respectively, when compared to preoperative levels.^{46,47}

The risk of recurrence is low, when using limited surgical procedures for benign cystic neoplasms and panNETs. For EN, PMSR, and DPPHR, a recurrent tumor was observed after a mean follow-up time of 2.4, 4.6, and 5.7 years, respectively, in 2.6%,⁴² 2%,⁴⁴ and 2.8%⁴⁸ of the patients respectively.

In conclusion: Patients suffering benign, symptomatic cystic neoplasms, and neuro-endocrine tumors of the pancreas should be treated using a parenchyma-sparing, local tumor resection whenever possible. Use of local resection procedures for benign tumors is associated with an improvement of procedure-related morbidity, when compared to classical PD and LP. The procedure-related advantages are a 90-day mortality below 1% and a low level of POPF B + C rates. Most importantly, the long-term benefits of the use of local surgical procedures are the preservation of the endocrine and exocrine pancreatic functions. The level of clinical evidence of parenchyma-sparing resections compared to standard procedures for benign pancreatic tumors is based on controlled prospective clinical trials, but randomized, controlled data are lacking. For patients undergoing surveillance with multiple EUS, CT, MRI and fine-needle aspiration investigations and who are burdened with fear of a progressing cancerous process of the pancreas, while under observation, the decision-making for cystic neoplasms and panNETs should be guided by the low surgical risk and the preservation of pancreatic metabolic functions when undergoing a limited, local, tissue-sparing procedure. To avoid under- or overtreatment, a new definition of criteria for local resection of benign cystic neoplasms and panNETs becomes essential to better balance operative morbidity with the potential of short- and long-term outcome benefits for the patients.

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