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Whipple Resection for Benign Tumors and Premalignant Neoplasms of the Pancreatic Head

Surgery-Associated Risk for Complications and Late Metabolic Morbidity Matters

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Pancreaticoduodenectomy (PD) is the gold standard for the surgical treatment of pancreatic head and periampullary cancer worldwide. Refinement and standardization of surgical techniques, high-quality intensive unit care, nonoperative interventions for complications, and surgical expertise in many centers have led to consider Whipple resection and pylorus-preserving PD with increasing acceptance as the appropriate surgical treatment for benign tumors and premalignant neoplasms of the pancreatic head.[1,2] However, the use of PD for a growing number of patients with benign, premalignant cystic, and neuroendocrine tumors questions the classical surgical approach of multiorgan tissue loss for a benign, local pancreatic disease. The goals of surgical treatment of benign and premalignant tumors include symptom relief by resection, prevention of malignant transformation of the tumor, low risk of surgery-associated complications, and maintenance of pancreatic and upper gastrointestinal (GI) tract functions. The classical Whipple resection requires tissue resection of the gastric antrum, duodenectomy, including the first jejunal loop, and resection of the biliary ducts and the pancreatic head. High-volume centers specialized in pancreatic surgery report a hospital mortality rate of ≤2%.[1,2] However, recently published results of large international mono- and multi-institutional studies of PD for benign tumors demonstrated an in-hospital mortality rate of 2–4 %[2,3] and a 90-day mortality rate of ≥4 %.[4,5]

Assessment of long-term endocrine functions following PD, using oral glucose tolerance testing, indicates a significant, late postoperatively persistent deterioration of the glucose metabolism. Data of high clinical evidence revealed that postoperative incidence of new-onset diabetes is observed in 14% to 20 % of patients.[6,7] Furthermore, PD leads to an escalation in diabetes. Patients with preoperative, noninsulin-dependent diabetes experience postoperative progression to insulin-dependent diabetes in up to 40%.[8] The resection of the duodenum, first jejunal loop, and pancreatic tissue is considered to be the main cause of persistent endocrine dysfunction after PD.[9] Loss of endocrine cells, which reside in the duodenum and upper jejunum, disruption of the interdigestive GI hormone release and insulin secretion by duodenectomy and duodeno-pancreatic neural connections, and loss of vagus-sensitive humeral factors are the main drivers of metabolic dysfunctions.

Measurements of the fasting and stimulated hormone levels in nondiabetic patients after PD reveals a significant reduction in the secretion of insulin, pancreatic polypeptide, and gastric inhibitor peptide, which control glucose metabolism, and of gastrin, secretin, and cholecystokinin, which regulate digestive fluid delivery. These indicate that the duodenum and proximal jejunum are the key metabolic signaling centers that coordinate GI hormone release and the pancreatic endocrine and exocrine functions. When measuring the exocrine pancreatic functions following PD for benign tumors, long-term pancreatic exocrine insufficiency was found in 30% to 45 % of patients.[10] Lifelong enzyme supplementation is required for every second patient after PD.

The development of nonalcoholic fatty liver disease was observed in 15% to 30% of patients when PD was applied for benign tumors.[11] Approximately 15% of patients with nonalcoholic fatty liver disease progress to steatohepatitis.

A recently published study used a national database to evaluate the overall prevalence of postoperative claims for diabetic medication and exocrine replacement therapy following 2848 PDs.[12] An increase in diabetic medication claims was observed from 19.0% to 28.7% for all patients and to 46.9% for 288 patients who underwent PD for benign lesions. The incidence of new diabetic medication claims among medication-naïve patients was 13.8% for PD after a postoperative median of 4.7 months. The need for pancreatic enzyme replacement therapy was 56.0% in all patients after PD and 39.2% for patients who underwent PD for benign lesions. Furthermore, the Columbia University Irvine Medical Center study suggests that young patients (<45 years) have a 5-fold increase in diabetes after PD compared with the US national diabetes statistics. The Columbia study provides convincing data that new-onset diabetes and new onset of exocrine pancreatic insufficiency persist following PD.

Although the study design was retrospective, based on postsurgical prescription claims for diabetic medication and enzyme supplementation, and included a heterogeneous population, the study confirms with data of a large patient group the observation that new endocrine and exocrine morbidity develops in a considerable number of patients following PD.

The most relevant question is how to use the data regarding surgery-associated early morbidity and endocrine and exocrine

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metabolic insufficiency following PD for clinical decision-making. Considering the evolution of local resections of benign pancreatic lesions, cystic neoplasms, and neuroendocrine tumors, it is important to elucidate the potential surgical and metabolic consequences of a major pancreatic resection compared with parenchyma-sparing procedures. Preservation of the pylorus in PD, widely introduced by Traverso and Longmire in 1978, was the first parenchyma-sparing procedure to improve GI morbidity after the classical Whipple resection by lowering the incidence of enterogastric reflux, dumping, and diarrhea. Duodenum-preserving pancreatic head resection (DPPHR), pancreatic tumor enucleation, and pancreatic middle-segment resection represent the most significant recent advances in pancreatic surgery for benign tumors. DPPHR and tumor enucleation for the surgical treatment of benign pancreatic head tumors have the advantage of preserving the duodenum and the bile duct and thereby preventing cholangitis, which is not a rare problem after distal bile duct resection. Prevention of new onset of exocrine and endocrine pancreatic dysfunction following DPPHR compared with PD has been evaluated with high clinical evidence based on randomized, controlled trials for inflammatory tumors[13,14] and prospective studies for cystic neoplasms and neuroendocrine tumors.[6]

We need more data from randomized, controlled trials comparing surgery-related postoperative complications and metabolic morbidity following DPPHR, tumor enucleation, and PD for tumors of the pancreatic head. The persisting metabolic morbidity in younger patients undergoing PD for benign pancreatic head tumors, as has been reported for branch-duct intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, solid pseudopapillary neoplasms, and serous cystadenomas, is underestimated. Surgeons should continue to learn more about the clinical relevance of local tumor factors and new surgical techniques that significantly reduce surgery-associated morbidity. The historical treatment standard for benign tumors of the pancreatic head is being challenged by the recent evolution of parenchyma-sparing, local resections of cystic neoplasms of the pancreas.

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