Editorial

Pancreatic fistula after pancreaticoduodenectomy—does surgical technique matter?

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Pancreaticoduodenectomy (PD) is the procedure of choice for the treatment of cancers of the pancreatic head and of periampullary region. Indications for PD have increased over time, since PD is performed also for the treatment of well-recognized pre-invasive tumors arising in this anatomical region (i.e., intraductal papillary mucinous neoplasms; IPMN) (1). PD is a complex procedure associated with a significant rate of postoperative morbidity and with a mortality rate around 2–3% when performed at high-volume referral centers (2). PD-related morbidity is mainly associated with the development of pancreatic fistula after pancreatic anastomosis (3). Pancreatic fistula is in fact the major determinant of several complications after PD including, infections up to severe sepsis, late bleeding from arterial pseudo aneurysm following arterial erosion due to pancreatic juice, intra-abdominal collections and abscesses, delayed gastric emptying, leakage of biliary and/or gastro-enteric anastomosis. For all these reasons pancreatic anastomosis has been defined as the "Achilles' heel" of pancreatic surgery. Surgeons dedicated to the pancreas have tried to overcome the issue of pancreatic fistula for many years and with different strategies. These efforts encompass the site of anastomosis (pancreatojejunostomy versus pancreatogastrostomy) and the anastomotic technique (duct-to-mucosa, invagination, dunking, Blumgart pancreatojejunostomy). Moreover some surgical details have been adopted as well such as the number of anastomotic layers (single versus double), the use of a single versus double intestinal loops, the use of internal versus external pancreatic stents, the application of fibrin glue, the administration of drugs to decrease pancreatic secretion (i.e., octreotide and its analogues), type of suture materials used. The number, site and type of drains placed during the operation were studied as well as their removal timing (4-11). However, there are no established strategies that proved to be effective in decreasing the rate of pancreatic fistula, and mainly, of clinically relevant pancreatic fistula—a pancreatic fistula with clinical impact on the postoperative course of the patient.

In this setting, Kim and colleagues (12) reported their experience with 50 consecutive PD with modified Blumgart anastomosis (BA). In their retrospective analysis, they found a 10% rate of postoperative pancreatic fistula (POPF), including 8% of grade B and 2% of grade C POPF. Only one patient died in this cohort, and Authors found a jejunal detachment from the pancreas stump, "because the jejunum was too thin compared with the thickness" of the pancreas. Therefore, they concluded that, irrespectively of modification of the BA (interrupted suture between the pancreatic parenchyma and jejunum) (12,13), the anastomosis between a thin jejunum and a thick pancreas as a risk factor for POPF. Clearly, this study has all the drawbacks of a retrospective analysis, mostly considering the small number of patients analyzed in a very long period (50 cases performed during a 7-year period for a mean of only 7.1 cases/year). It is unclear if a single surgeon

performed all the procedures and if this was the only anastomotic technique used in the study period, as the risk of selections bias would be very high. The use of anastomotic stent was different case by case and there are no data regarding the administration of somatostatin analogues. Moreover, it is unclear how the texture of the pancreatic gland as well as the size of main pancreatic duct influenced the development of POPF. There are no clear data regarding the postoperative management of the patients considered, and it is unclear if intraoperative/postoperative techniques and strategies changed over time. Finally, it is impossible to draw conclusions regarding a specific anastomotic technique by evaluating the fate of a single case. Although we agree that retrospective studies can give insights into some issues, the scientific applicability of the results of this study is minimal.

This allows us to make some final considerations. Firstly, surgeons focused their attention of specific technical issues to solve the *unsolved problem of pancreatic fistula*. However, the most important risk factor for pancreatic fistula is the pancreas itself (i.e., soft pancreas with small main pancreatic duct) (14), and therefore studies should be focused on mitigation strategies in order to decrease the clinical impact of POF rather than to prevent it. Secondly, in order to achieve this mitigation strategy, it is of paramount importance the experience of the surgeon and even more relevant, of the center where pancreatic surgery is performed (15,16). This is particularly true for postoperative mortality. In fact, a linear correlation between surgeon/hospital volume and mortality has been largely demonstrated. Finally yet importantly, there is a methodological problem. Retrospective, single center, maybe single surgeon, studies have too many drawbacks, but also randomized controlled trials (RCT) may have significant limitations. In a systematic review and meta-analysis of randomized controlled trials (RCT) comparing pancreatojejunostomy (PJ) and pancreatogastrostomy (PG) we analyzed ten RCTs including 1,629 patients (10). The most relevant results of this work was the evidence of a significant heterogeneity regarding the definitions of POPF, anastomotic techniques, perioperative management, and the characteristics of pancreatic gland among the different trials. We found that that PG and PJ were comparable in term of overall and clinically significant POPF, overall morbidity, reoperations, and mortality.

In order to appropriately assess benefits and pitfalls of an anastomotic technique in the setting of pancreatoduodenectomy, only well-planned and powered RCT should be considered. These studies should be mainly focused to high-risk patients (i.e., patients with soft pancreas) and they should include standardized and homogeneous techniques, standardized and universally accepted definitions of POPF/complications as well as standardized perioperative/postoperative management. The experience of participating surgeons and hospitals should be also considered in order to avoid bias related to poor experience of operating surgeons of to a low hospital volume. In this setting, the cooperation among high-volume referral centers will be indispensable.

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Footnote

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