



Total pancreatectomy in patients at high risk of postoperative pancreatic fistula (POPF)

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The morbidity associated with postoperative pancreatic fistula (POPF) remains a dominant factor that influences postoperative outcomes in patients undergoing pancreaticoduodenectomy (PD). Although most patients who develop a clinically relevant (CR)-POPF can be effectively treated with antibiotics and/or radiological drainage, a subset of patients who develop organ failure or require invasive intervention (e.g., embolization or surgery) have a high risk of mortality (1). The mortality associated with PD has improved over recent decades, despite a constant incidence of POPF, and is probably due to multiple factors, including surgical technique, centralization of pancreatic surgery, and advances in perioperative management (2). Given the potential impact of POPF-related morbidity, particularly in older, frail patients, this topic remains a focus of research for pancreatic surgeons.

The risk factors for POPF are well established and have been incorporated into various scoring systems, but most risk factors are essentially non-modifiable (i.e., body mass index, pancreatic duct width, pancreatic texture). Rather than preventing POPF, there has been a shift of focus towards reducing the severity and/or impact of POPF by optimising postoperative management, including prompt recognition of POPF, early cross-sectional imaging and active intervention (3). An alternative strategy adopted by some pancreatic surgeons is to perform a total pancreatectomy (TP) in patients at high risk of CR-POPF (4,5), which clearly eliminates the risk of POPF, at the

expense of the long-term consequences of endocrine and exocrine failure. Whether the short-term benefits of TP can be justified is a matter of debate. The authors of a recently published nationwide Dutch study addressed this question by evaluating the outcomes of PD in patients at high risk of CR-POPF (6). The authors defined high risk according to a recent International Study Group for Pancreatic Surgery (ISGPS) definition based on pancreatic duct diameter <3 mm and soft pancreatic texture. The incidence of POPF in this study of over 1,400 patients was 30% and, as expected, POPF was associated with an increased mortality rate of (6.3% *vs.* 3.5%; $P=0.016$). Only four patients underwent prophylactic TP during the study period [2014–2021], indicating that this strategy is rarely considered in the Netherlands at present. The authors concluded that the overall hospital mortality rate of 4.1% in patients undergoing PD with high-risk anastomoses was acceptable and does not justify TP in this patient cohort. However, the authors also reported that patients with American Society of Anesthesiologist (ASA) >2 and those who underwent extended resections had significantly increased hospital mortality (10.7% and 11.3%, respectively). They have suggested that these subgroups may benefit from TP and recommend further research in this area.

The study defined patients as high-risk based on the ISGPS definition (7). However, this relies on subjective assessment of pancreatic texture, which is an important limitation, and it may have been more appropriate to use

an objective risk score (e.g., alternative Fistula Risk Score or Birmingham Risk Score) (8,9). The operating surgeon's experience is likely to be a major factor in determining the incidence and severity of POPF, although the evidence to support this hypothesis is relatively limited. The association between centre volume and outcomes after pancreatic surgery is well established and is probably related to the experience of both operating surgeon and the wider team (10,11), in addition to optimised postoperative pathways that may lead to reduced 'failure to rescue' rates (12,13). One study that evaluated the learning curve of the pancreatic anastomosis using risk-adjusted CUSUM analysis found a significant difference between surgeons based on experience, with a learning curve of approximately 50 procedures to reduce the POPF rate (14). Importantly, the study by Theijse *et al.* did not evaluate either surgeon experience or centre volume on the incidence or severity of POPF. Another major limitation of this study was the fact that one-third of patients who underwent PD during the study period were excluded due to missing data on pancreatic duct width or texture, and this is likely to have introduced selection bias into the study. Due to the very small number of prophylactic TPs performed in the Netherlands, it was not possible to perform a comparative analysis between PD and TP.

A single-centre retrospective study from Verona compared both short-term outcomes and quality of life (QOL) after high-risk pancreatic anastomosis and TP in almost 600 patients, and found that TP was associated with a significantly shorter length of hospital stay (10 *vs.* 21 days; $P < 0.05$) whilst mortality was similar between groups (15). The majority of QOL parameters were similar between groups after 1 year, although as expected, diabetes-specific QOL was worse after TP (15). The impact of TP on QOL was the focus of a systematic review by the Dutch Pancreatic Cancer Group in 2019 (16). This study included data from over 1,500 patients with a longer follow-up period (median 28.6 months) than the Verona study (15) and found that TP was associated with a significantly reduced QOL compared to the general population, predominantly related to exocrine failure (16). However, there is a lack of data comparing long-term quality of life outcomes between high-risk PD and TP, and this is likely to require a multi-institutional study from high volume centres. A major limitation of retrospective studies that compare long-term outcomes between high-risk PD and TP is an inherent selection bias since high-risk PD are more likely to be performed for patients with better prognosis tumours

(e.g., ampullary cancer) (6). A prospective study would be necessary to overcome this issue.

In summary, the study by Theijse and colleagues has reported acceptably low mortality rates after PD in patients with high-risk pancreatic anastomoses, despite an overall high incidence of POPF in this nationwide study. The authors have questioned whether TP can be justified in all high-risk patients but have suggested that TP may be considered in patients with significant comorbidity or after extended resections, due to the higher POPF-related mortality rate in this subgroup. Further research is required to evaluate the impact of centre volume on POPF-related outcomes, particularly in medically high-risk patients undergoing complex resections.

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