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Comment on: Pancreatectomy With Islet-Autotransplantation As Alternative for Pancreatoduodenectomy in Patients With a High-Risk for Postoperative Pancreatic Fistula: The Jury Is Still Out

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We would like to congratulate Balzano et al[1] on their randomized controlled bicenter PAN-IT trial wherein total pancreatectomy (TP) with islet-autotransplantation (IAT) was studied as an alternative for patients undergoing pancreatoduodenectomy (PD) with a high-risk for developing postoperative pancreatic fistula (POPF). However, we have some concerns regarding the authors' final conclusions that TP-IAT may become the standard treatment in candidates for PD with a high risk for POPF. Our concerns center on (1) the primary endpoint of the PAN-IT trial, (2) the lack of assessment of patient-reported outcomes, and (3) the quality of diabetes control.

First, it is questionable if postoperative morbidity is the optimal endpoint in a trial that aims to elucidate the role of TP(-IAT) as alternative to PD with a high risk for POPF. How much morbidity should be prevented to justify a lifelong apancreatic state? Indeed, TP-IAT improved the primary endpoint (ie, 90-day overall complication rate) by avoiding POPF, but the 90-day mortality did not differ statistically significant despite a clinically relevant difference (9.7% after PD vs 3.3% after TP-IAT), which is line with recent retrospective single-center series.[2,3] However, the mortality after TP(-IAT) in the daily clinical practice may be substantially higher. A recent prospective European international multicenter study including 277 patients who underwent TP found a 90-day mortality rate of 7.6%, which increased to even 11.9% in centers performing less than 60 PDs per year.[4] Moreover, the recent Dutch PORSCH trial demonstrated that postoperative mortality can be reduced after PD regardless of hospital volume due to the implementation of an algorithm for early detection and treatment of POPF.[5] As a consequence, the vast majority of the clinically relevant POPF can be managed either conservatively or with minimally invasive interventions.[5]

Second, patient-reported outcomes including quality of life over time are highly relevant endpoints when determining the role of TP(-IAT) in our opinion. Surprisingly, quality of life was not evaluated over time, while the prospective nature of the PAN-IT trial offered a unique opportunity to investigate this properly. This should be included in future prospective studies. Although the interest in TP for this indication has been renewed in recent years by the improved morbidity and mortality after TP in high-volume centers[4,6] and more adequate management of the associated metabolic insufficiencies, the related adverse events remain substantial.[7] Quality of life on the middle- and long-term after TP is reduced in comparison to the general population.[8,9] IAT after TP only (mostly temporarily) controls the endocrine insufficiency partially, whereas exocrine insufficiency remains a challenge. This is especially relevant for the currently studied indication of TP(-IAT) since patients with a high risk for POPF after PD often have long-term survival because of benign/ premalignant pancreatic diseases.

Third, the quality of diabetes control and insulin independence obtained by TP-IAT. Already after 1 month, glycemic control as measured by hemoglobin A1c was worse in the TP-IAT group and at the end of follow-up (median follow-up of 388 days), only 6.7% of patients after TP-IAT were independent of insulin versus 80.6% of patients after high-risk PD. The authors argue that the absence of serious hypoglycemic events is explained by the remaining graft function. However, long-term results are missing, while these are highly important considering the likelihood that the graft function will further decrease over time. An alternative for or additive to IAT might be the bihormonal artificial pancreas, for which we recently demonstrating promising results.[10]

In summary, the PAN-IT is a high quality randomized trial that provides quite relevant insights, but in our opinion does

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not confirm that TP-IAT may become the standard treatment in patients with a high risk for POPF after PD. We question whether a 30% absolute risk reduction of short-term postoperative morbidity justifies a 73% absolute risk increase of lifelong insulin dependence and, most likely, decreased quality of life. Furthermore, early POPF recognition and step-wise minimally invasive management have an important role in the improvement of both morbidity and mortality after PD. Only future large, randomized studies with mortality and quality of life as primary outcome can answer this question.

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