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Comment on Total Pancreatectomy With Islet Autotransplantation as an Alternative to High-Risk Pancreatojejunostomy After Pancreaticoduodenectomy: A Prospective Randomized Trial

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We thank Dr Leo Hans Buhler and colleagues for their keen interest in our study[1] and the editor for the opportunity to respond to the issues that were raised. The PAN-IT trial recruited patients with pancreatic ductal adenocarcinoma (PDAC) and various other neoplastic disorders. Buhler and colleagues pointed out that in our study the proportion of patients with PDAC was 9 of 31 (29%) versus 5 of 30 (16.7%) for the pancreaticoduodenectomy (PD) and total pancreatectomy (TP-IAT) groups, respectively, and suggested that this difference (although nonsignificant: P = 0.36, Fisher exact test) may have favored TP-IAT over PD when assessing the outcomes of our trial, particularly disease-specific and overall survival.

As reported in the article, to avoid imbalance in the severity of neoplastic disease between the 2 groups, we allocated patients to study treatment by minimization, to balance periampullary adenocarcinoma (including PDAC, ampullary adenocarcinoma, distal bile adenocarcinoma, and duodenum carcinoma) versus other neoplastic, benign or borderline lesions in the 2 groups. Randomization was indeed successful, as the proportion of patients with periampullary adenocarcinoma was 24 (PDAC n = 9) of 31 (77.4%) versus 21 (PDAC n = 5) of 30 (70%), for PD and TP-IAT, respectively (P = 0.57, Fisher exact test). To respond to the concern of Buhler and colleagues, we performed additional analyses of our data. However, numbers in the presented subanalyses are low and, therefore, results should be taken with caution, this being the reason why they were not presented in our original article.

1. In an intention-to-treat subanalysis, morbidity rates in patients with PDAC versus other periampullary adenocarcinoma (other K) were 88.9% versus 100% (P = 0.37), respectively, after PD and 60% versus 68.8% (P = 1.00) after TP-IAT, that is, patients with PDAC had similar morbidity rates than patients with other K in both treatment groups. Therefore, the prevalence of PDAC within treatment groups did not influence our primary endpoint, that is, morbidity.
2. In the Cox-regression analysis used in our original article to estimate overall and disease-specific survival for both treatment groups in patients at high risk of POPF (group A and B), we included PDAC diagnosis as an additional covariate. In this post hoc analysis, we confirmed a trend toward a reduction of mortality, even when taking into account PDAC diagnosis. For simplicity, we report only disease-specific survival data of this analysis: risk for death TP-IAT versus PD: HR = 0.57 (0.21–1.54), P = 0.27; PDAC versus others K: HR = 1.99 (0.77–5.1).
3. Similarly, in the Cox-regression analysis used in our original article to estimate overall and disease-specific survival for both treatment groups in all patients (groups A, B, and C), we included PDAC diagnosis as an additional covariate. In this post hoc analysis, we again confirmed a trend toward a reduction of mortality, even when taking into account PDAC diagnosis. For simplicity, once more we report only disease-specific survival data of this analysis: risk for death TP-IAT versus PD: HR = 0.46 (0.21–1.54), P = 0.093; PDAC versus others K: HR = 1.58 (0.73–3.4), P = 0.24].

Furthermore, we understand and share the concerns of Buhler and colleagues on the risk of "SPIN"; however, we do not believe our results were presented so to raise the issue of SPIN. SPIN in RCTs is defined as "specific reporting strategies to highlight that the experimental treatment is beneficial, despite a statistically nonsignificant difference for the primary outcome."[2] In our trial, the primary outcome was indeed significant and we do considered an extremely positive result the finding of no significant differences in disease-free survival, site of recurrence, disease-specific survival and overall survival between PD and TP-IAT since the fear of infusing malignant cells with the islet preparation has been limiting the use of IAT for patients with malignancy. Moreover, we clearly stated that the trend toward a reduction of mortality was a post hoc finding and, as such, was not reported in the abstract. Finally, we reported among the limitations of the study the heterogeneity in term of indication for pancreatectomy and that our study was underpowered to detect significant difference in survival. As commonly accepted, we have used our post hoc analysis to suggest new working hypotheses and our recently started TP-IAT-01 trial (NCT05116072), which hypothesize that TP-IAT rather than PD may improve access to adjuvant chemotherapy, will hopefully provide further evidence for or against this hypothesis.

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