French Editorial Commentary from the ACHBPT

Pancreatic enucleation: a valid surgical option with encouraging quality of life

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In their study "Pancreatic Enucleation Patients Share the Same Quality of Life as the General Population at Long-Term Follow-Up", Giuliani *et al.* (1) assess short- and long-term outcomes including quality of life after pancreatic enucleation (PE).

PE aims to preserve endocrine and exocrine function while ensuring surgical ablation of a presumed benign pancreatic tumor (neuroendocrine tumors, mucinous cystadenoma, serous cystadenoma, branch duct intraductal papillary mucinous neoplasms and solid pseudopapillary tumors). However, the rate of postoperative pancreatic fistula is up to 70%, particularly when the tumor is localized at the head and is close to the main duct (2-6). To assess if this advantage is perceived by patients, quality of life was considered knowing that there is no literature data concerning the quality of life following PE unlike the other pancreatic resections (7-11).

Data collected were from consecutive patients who underwent PE from January 2010 to December 2019 at the Department of General and Pancreatic Surgery, Pancreas Institute, University of Verona Hospital Trust in Italy. A prospective collection of pre-, per- and post-operative data was performed with a retrospective analysis. Surgical outcomes were measured according to Clavien-Dindo classification and quality of life was assessed through EORTC-C30 and EORTC-Pan26 (European Organization for Research and Treatment of Cancer) questionnaires. The control group was composed of healthy people from general population who were matched to patients 1 to 1 using propensity score based on criteria of age, gender, body mass index (BMI) and history of previous malignancy. They volunteered on social media networks. There were 80 questions on four questionnaires necessitating 10 to 15 min to complete. The first questionnaire gathered general characteristics; EORTC-C30 and EORTC-Pan26 assessed general and pancreatic symptoms; the last one detected new-onset of diabetes mellitus following pancreatic resection and pancreatic exocrine insufficiency assessed with the use of pancreatic enzymes. Three questions were not administered to controls (digestive symptoms, side-effects and satisfaction with the health care) and were excluded from the comparative analysis.

In total, 81 patients underwent PE: 48 open surgeries (59.3%), 22 laparoscopic (27.2%) and 11 robot-assisted (13.6%). The minimally invasive technics were often used for left pancreatic lesions (P<0.005). Open surgeries lasted longer (180 *vs.* 150 min, P=0.023), without a significant difference when analyzed in subgroups of tumor location (P=0.217). Sixty-five patients (80.2%) presented neuroendocrine tumors with 78.3% of G1 (Ki-67 ≤2%).

Surgical morbidity was 48.1% and the rate of major complications Clavien-Dindo 3 or over was 16%. In-hospital mortality was 0%. The rate of pancreatic fistula was 21% with 19.8% of biological fistula; post-operative hemorrhage was 9.9% and delayed gastric emptying rate was 4.9%. The median hospital length of stay was 8 days and was significantly longer for open surgeries (P=0.023).

The questionnaires were returned at a median follow-up of 74.2 months. Five patients (7.1%) presented new-onset of diabetes mellitus following pancreatic resection independently from their age without significant difference compared to the control group (2.9%, P=0.441). No difference was found regarding the tumor location. Seven patients (10%) developed pancreatic exocrine insufficiency with median intake of pancreatic enzymes of 60,000 UI per day (P<0.005).

When analyzing the quality of life, after propensity score, 70 patients were selected in each group.

The global quality of life score was slightly higher for patients who underwent surgery without significant difference. The global health status score was 68.1 [standard deviation (SD) 23.9] and all functioning scale scores were up to 80. The highest symptom scores concerned fatigue and insomnia: 19.4 (SD 21.7) and 20.0 (SD 27.5) respectively. Among pancreas-specific symptoms, flatulence and sexuality scored the highest: 22.9 (SD 28.1) and 19.5 (SD 25.5) respectively. All functions and symptoms were comparable apart from 2 EORTC-Pan26: worries for the future and body image, P<0.05. This could be explained by the history of pancreatic surgery that could modify the body image and enquire about survival.

The authors demonstrated through this study that despite a high post-operative morbidity, PE provides excellent long-term outcomes, notably for quality of life, and should be considered as a valid surgical option for non-malignant small tumors. This should encourage surgeons to propose PE when it is indicated.

The current study seems to be the only one focused on quality of life after PE. Following value-based healthcare pathways evaluation, patient-reported outcomes are increasingly integrated to clinical results as morbidity. The evaluation of surgical technics should no longer be only based on post-operative results—important to surgeons—but should also consider patient-reported outcomes that matter to patients (12,13). Finally, patients stay at the center of the medical care and their point of view are substantive.

The EORTC-C30 and EORTC-Pan26 questionnaires are usually used for malignant diseases, unlike the use in this study population. However, they allow comparisons between pancreatic resection outcomes (8,9,11). Van Dijk *et al.* (8) conducted a systematic review on the impact of cephalic duodenopancreatectomy for cancer on quality of life and showed that it declined for physical and psychological functions the first months after surgery before regaining the pre-operative baseline at 3 to 6 months after. Pulvirenti *et al.* (9) demonstrated that elderly have more risk of post-operative complications after total duodenopancreatectomy but have a better quality of life compared to young patients.

PE is performed in limited indications and this could justify the small sample of study population despite the long period of recruitment. In addition to the monocentric nature of the study, the results are promising but we can hardly extrapolate them to other centers. The elaboration of standardized questionnaires could allow this kind of comparison encouraging centers to reach excellence of care. Furthermore, symptoms and quality of life data were collected for each patient of the study population at one point of the follow-up, at different moments depending on the patient, and over a long period of time—between 43.4 and 109.3 months after PE. Gathering these elements according to an established timeline of the follow-up would be more informative to assess symptoms and quality of life scores as proposed in value-based standardized questionnaires, with more reliable prospective data collection.

The analysis of quality of life and of EORTC-C30 and EORTC-Pan26 outcomes of the 70 patients who answered the questionnaires was done for 4 sub-groups according to the location of the pancreatic lesion (Head/Up *vs.* Body/Tail) and the surgical approach (Open *vs.* Minimally invasive). Samples were small: 27 Head/Up-Open; 5 Head/Up-Minimally Invasive; 16 Body/Tail-Open; 22 Body/Tail-Minimally Invasive. This could explain why only 2 criteria were statistically significant with a low power test. The surgical approach could have influenced the functional outcomes. However, the comparison of patients to healthy controls could not reflect the impact of the surgical approach neither the location of the tumor.

Besides, quality of life outcomes in this study are questionable. Indeed, it is unclear if the better quality of life is linked to sparing pancreatic parenchyma or rather to better prognosis of benign lesions. In addition, among the group of patients who underwent PE in this study, only one patient presented a grade C pancreatic fistula—1.2% of the study population. This low rate could be a bias in the favorable long-term outcomes concluded in this

study because of the reduced clinical impact of a surgical re-intervention and/or organ-failure.

Finally, PE offers excellent long-term outcomes despite significant morbidity. Authors recommend PE as the first surgery choice for non-malignant pancreatic lesions.

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