



Minimally invasive pancreatic enucleation—the need for further evidence

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I read the invited comments made on our piece with great interest (1). At the same time, I greatly appreciate the opportunity to share some further considerations on the argument.

Although we aimed at comparing the relative outcomes of minimally invasive *vs.* open pancreatic enucleation, Yiannakopoulou asserts that the main question is whether the risk of postoperative pancreatic fistula (POPF) is higher following enucleation or following formal parenchymal resection.

In reading such comment, some perplexities arise.

In fact, the main question claimed by the author not only was out of the purpose of our study, but also has already several and concordant answers within the current literature (2-4). Indeed, despite the lack of high-level evidence such as randomized trials, most of the investigations on this topic have indicated higher incidence of POPF following enucleation as compared to formal parenchymal resection (2-7).

Hüttner *et al.* (2) recently published a well-conducted systematic review with meta-analysis of the literature comparing enucleation *vs.* standard resection for pancreatic neoplasms. The author included 22 observational studies aggregating the data of nearly 1,150 patients. Overall, the analysis of POPF revealed significant superiority of standard resection over enucleation [odds ratio (OR): 2.1, $P < 0.001$]. This difference was also confirmed at the specific analysis combining only data coming from studies that applied the international definition of POPF (8) (OR: 2.15, $P = 0.003$ and OR: 1.93, $P = 0.01$, for all grades POPF and grade B/C POPF, respectively), and when only high-volume studies were considered (OR: 1.72, $P = 0.12$).

Similarly, Zhou *et al.* (6) have conducted a comprehensive meta-analysis describing all available data on pancreatic enucleation including >1,300 patients from 27 studies. Twelve of the included studies (more than 1,000 patients) compared enucleation with typical resection. Patients receiving enucleation had significantly higher incidence of both POPF (OR: 1.96, $P < 0.001$) and clinically relevant POPF (OR: 2.07, $P = 0.002$) than those undergoing conventional resection.

On the other hand, Yiannakopoulou sustains that “*a matter of controversy still remains on the comparative incidence of POPF following MIS vs. open enucleation*” (1). I definitely agree with her. Actually, the purpose of our study was to investigate whether the available literature did indicate any difference on clinical outcomes (and POPF in particular) in the case of pancreatic enucleation. Overall, the considerations shared by Yiannakopoulou on the feasibility and advantages of pancreatic enucleation resume well our findings, which substantially confirm the procedure as a high morbidity/low mortality (2,6-9).

Conversely, it has been also asserted that “*it would be anticipated that minimally invasive surgery led to lower rates of POPF*” as compared to conventional surgery. Apparently, this is not consistent with the previous assumption, and I worry about the scientific basis of this assumption, which likely takes place from an erroneous interpretation of the current data from the available literature.

Already in 2004 Assalia and Gagner published their pioneering experience on 17 laparoscopic pancreatic surgeries (both enucleation and formal resections) for endocrine tumors of the pancreas (10). Overall, the authors reported excellent results encouraging the implementation

of minimally invasive surgery (MIS) for pancreatic surgery. The authors also pooled the existing experiences recorded in the literature concerning both MIS and conventional surgery on the same argument. Interestingly, they found that while minimally invasive distal pancreatectomy (DP) resulted in a lower incidence of POPF as compared to open DP (5.1% *vs.* 12.5%) this difference was inversely present with regard to tumor enucleation (30.7% *vs.* 28.8%, respectively).

About 10 years later, Song *et al.* reported on one of the largest single-center experiences on pancreatic enucleation (11). The authors aimed to investigate immediate and long-term results on a consecutive series of patients and to compare the relative results of laparoscopic *vs.* conventional open procedures. There were no substantive differences between the preoperative characteristic of patients receiving MIS and patients undergoing open surgery. On the contrary, there was a significant difference concerning tumor location. In the open group there were significantly more patients with tumor located in the head and uncinate process compared to patients in the laparoscopic group, which had tumors more frequently located in the neck, body and tail of the pancreas. The occurrence of POPF was diagnosed and evaluated according to the International Study Group on Pancreatic Fistula (8), with grades B and C defined as clinically relevant events. The overall incidence of POPF and clinically relevant POPF was 20% and 9.2%, respectively. Interestingly, despite more unfavourable tumor location, the incidence of clinically relevant POPF was higher in the laparoscopic group than in the open counterpart (10.7% *vs.* 13.5%, respectively). The authors concluded confirming the safety and effectiveness of pancreatic enucleation, suggesting laparoscopic enucleation as a feasible and safe procedure only in selected patients.

Belfiori *et al.* recently published an interesting, retrospective bi-institutional analysis of 71 patients with benign, sporadic insulinoma receiving pancreatic enucleation (12). The authors did compare the relative results of MIS (both standard laparoscopic and robotic) *vs.* conventional surgery (15 *vs.* 56 patients, respectively). Overall, there was not any statistically difference between the two approaches in terms of postoperative morbidity and particularly in terms of POPF and clinically relevant POPF. Nevertheless, it has to be considered that MIS cases were likely to be more technically advantageous, as the proportion of tumor located in the pancreatic body and tail was 73% *vs.* 39%, for MIS and open surgery, respectively.

In the abovementioned systematic review with meta-analysis by Zhou *et al.* (6) the authors also performed a number of sub-analyses on different aspects of surgical resection including one evaluating MIS *vs.* conventional surgery for pancreatic enucleation (about 150 patients included from 4 studies). Beside a significant advantage of MIS over open surgery in terms of operative time and length of hospital stay, the authors found out that MIS was associated with an OR of 1.13 and 1.66 of developing POPF and clinically relevant POPF, respectively.

Hence, it is clear that during the last years in a number of scientific reports some concerns have been raised about the risk of POPF following minimally invasive pancreatic enucleation. Starting from this presupposition, we aimed to pool the currently available evidence within the medical literature. In fact, probably due to increased experience in the application of minimally invasive pancreatic surgery along the recent years and availability of new technologies (5,13) we were able to collect more than 400 patients from 8 comparative studies (7). Interestingly, the use of minimally invasive surgery compared favourably with standard surgery in terms of POPF (OR: 0.81), although this difference did not attain statistical difference ($P=0.45$). Our review was the first analysis to identify, summarize and combine the published evidence focusing on the clinical outcomes and POPF in particular. Moreover, it was the first to indicate that according to the available data, the incidence of POPF is not superior following MIS than following conventional surgery.

According to the author, “*the methodology of our systematic review with meta-analysis raises several issues*”. The limitation of literature data, the lack of randomized evidences and the heterogeneity between the studies have been indicated as main concerns.

Firstly, these aspects are not due to the quality of the methodology employed, but rather in connection with the relative lack of robust data within the inherent literature. It is well-known that the reliability of evidence derived from meta-analyses depends on the design of the included studies, their specific risk of bias and likelihood of publication bias (14).

In addition, it is important to recall that case reports are, by definition, noncomparative in nature and that their certainty in evidence is very low, essentially due to the high risk of selection bias and reporting bias (14). Thus, is methodologically impossible (and incorrect) (15-17) to collect them within the context of a meta-analysis. Moreover, with particular reference to laparoscopic pancreatic

surgery, the considerations on the aim of case reports of presenting a surgical complication is improbable. Within the aforementioned paper by Assalia and Gagner (10), the authors also reported on all the available literature on the argument aggregating nearly 100 cases of all existing laparoscopic surgeries from limited case series (up to 10 patients) and case reports. By analyzing thoroughly the data presented, it was clear that almost all experiences (despite mostly preliminar) of laparoscopic enucleation did not report on surgical complications, but rather resulted in favorable outcomes, in terms of both procedural details and postoperative morbidity.

To conclude, Yiannakopoulou writes that “*the goal of minimally invasive approaches by laparoscopy or robotic assisted surgery should be the decrease of the rate of pancreatic fistula and all the other complications of the minimally invasive pancreatic enucleation*”. This statement is questionable and easy to misinterpret. If the author means that the aim of minimally invasive surgery should be the decrease of the rate of POPF in the case of pancreatic enucleation, I totally disagree with her, because this is the purpose of any surgery, regardless of the technique employed! Actually, the application of the minimally invasive method (both conventional and robotic laparoscopy) has the purpose of reproducing the same maneuvers we perform via celiotomy while providing patients with the well-known advantages resulting from reduced wall-related trauma.

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appropriately investigated and resolved.

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