Comment on: oncologic outcomes after robotic pancreatic resections are not inferior to open surgery

Antonio Mimmo[1], Tullio Piardi[2]

[1]Department of Hepatobiliary, Pancreatic and Digestive Oncological Surgery, Robert Debré University Hospital, University of Reims Champagne-Ardenne, Reims, France; [2]Research Unit Ea3797 VieFra, Department of Hepatobiliary, Pancreatic and Digestive Oncological Surgery, Robert Debré University Hospital, University of Reims Champagne-Ardenne, Reims, France

Correspondence to: Antonio Mimmo, MD. Department of Hepatobiliary, Pancreatic and Digestive Oncological Surgery, Robert Debré University Hospital, University of Reims Champagne-Ardenne, Rue du Général Koenig, 51100 Reims, France. Email: amimmo@ch-reims.fr.

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We read with interest the recently published article of Girgis *et al.* (1). The paper is a non-inferiority study regarding robotic versus open approach in the pancreatic resection for pancreatic adenocarcinoma (PDAC). The authors examined post-surgical complications, overall survival (OS) and the effect of surgical approach for the access to adjuvant chemotherapy (aCHT). According to the majority of scientific literature, aCHT improves the rate of survival in patients after resected PDAC. After a pancreatectomy, post-surgical complications limit the access to aCHT and, consequently, they reduce the OS (2).

The study was a retrospective single-center review of patients who underwent robotic or open pancreatectomy for PDAC from 2011 to 2016 with 24-month follow-up. Their results were based on 226 robotic and 230 open pancreatectomies. The patients included in the robotic group were the patients operated after that the surgeons had achieved the institutional robotic learning curve, in order to minimize selection bias in the robotic cohort. No significant differences, between two groups, were identified in major complications or to access to aCHT. Robotic pancreatectomy patients had a shorter length of hospital stay, with lower wound infection and transfusion rate. The authors reported an improved OS in favor of the robotic cohort (25.6 *vs.* 23.9 months; P=0.055). The authors concluded that the oncologic outcomes of robotic pancreatic surgery (RP) were similar to open pancreatic surgery. RP was a positive predictive factor in improving survival. They speculated that improving survival in the RP is linked to decrease blood loss and transfusion.

We congratulate the authors because this paper is one of the most comprehensive articles published concerning RP for PDAC, in particular regarding Whipple procedure (WP) and Appleby procedure (AP), even if it is a retrospective study. The aim of the study was challenging because the authors hypothesized that RP, in terms of perioperative morbidity, receipt of aCHT, and OS would be similar to the open approach.

Four categories were compared: overall pancreatic resection (OPR), WP, distal procedure (DP) and AP. This database of 456 OPR is represented by 79.2% (n=361) of WP, 16% (n=73) of DP, 4.8% (n=22) of AP. We can only underline some weaknesses: the first is that all surgical procedures originated from a single center experience, the second is that there is not any explication regarding the number of patients needed to achieve the learning curve for the robotic approach. In, addition, the size of two groups in each category is not sufficient for the type of analysis made, as it has been properly underlined by the authors. The category of OPR was not the representation of a homogeneous procedure, but rather it was mainly focused on the WP. In this kind of study, in order to analyze the difference between two groups concerning the loss of chance to access to aCHT and OS, we estimate it would require a sample size of 10^4 patients. Concerning differences in severe complications rate, a simple size of 10^3 patients would be required to show some difference between the two groups. In order to bypass the problem of the sample size in both analyses, we suggest conducting a propensity-match analysis in a multi-center study setting (2,3).

In regards to the results, we have found some significant differences between each group. Firstly, the type of lymphadenectomy: standard or extensive for robotic approach? The authors did not report what type of procedure was performed but they reported the number of lymph nodes (LN) harvested in the WP, 25.9 (mean) in the open *vs.* 31.9 in the robotic surgery. In the DP the mean of LN harvest was respectively 24.8 and 28.8. It seems that robotic magnification and dissection may considerably improve the effectiveness of lymphadenectomy, especially in WP. In any case we must not lose sight of the fact that the role of lymphadenectomy has been well described and that even if the 3D dimension allows the structures to be clearly highlighted, an extended lymphadenectomy does not correspond to a better survival (4,5). In the literature it has been reported that the number of LN harvest required is 15 LN for the WP and 15–20 LN for DP (4,5). Another interesting point is the operative time. In all groups, the robotic approach improves surgical speed significantly, especially in DP and AP. This is probably linked to best exposition and efficiency of robotic magnification. We know that the total operative time could be modified according to the type of robotic technology and the time of docking, which naturally improves during the learning curve (6). In this regard, it would have been interesting if the authors had described the surgical technique of the different procedures and their stratification during the learning curve to better analyze the operative time and secondarily the post-operative complications.

In the paper, no significant differences were found in the perioperative morbidity of pancreatic surgery regarding the surgical approach. The predicting factor for severe complication in the multivariate analysis was the Charlson Comorbidity index (CCi), but when it was stratified for age. The absence of the description of the surgical techniques is an important missing element. In literature, for example, a large prospective multicenter randomized trial, comparing mini-invasive approach versus open approach for pancreatoduodenectomy, was prematurely stopped due to more complication-related deaths in laparoscopic pancreatoduodenectomy than open pancreatoduodenectomy (7). One of the possible reasons was that the increase of surgical complications was related to the use of 3/0 V-loc barbed sutures in the pancreatic-jejunostomy. In this analysis of severe post-operative surgical complications (24.5% *vs.* 29.8%, respectively in robotic *vs.* open approach), we don't know if Girgis *et al.* utilized the same technique in the robotic or open approach (7-9). Certainly, a point in favor of the robot compared to laparoscopy and perhaps to open surgery is that we also associate the magnificence of vision with the 360° use of the different arms: that is, the possibility of performing an anastomosis even better than open surgery because it is more meticulous. Considering that pancreatic anastomosis represents a challenge for surgeons dealing with minimally invasive pancreatic surgery, it would have been interesting to analyze the technique and report the pancreatic fistula rate which was not the case in this study.

Concerning the access to aCHT, in order to analyze the loss of chance for OS, no significant differences were found between the two categories of surgical technique. Every technique led to start the aCHT behind 90 days from the surgery, according to international guidelines. The difference was evident in the open AP where the patients started the CHT after a mean of 145 day which we possibly think was linked to the complexity of surgical procedure: no explanation was given concerning higher time of aCHT in AP. In the paper, the predicting factors to limit aCHT in the multivariate analysis were age, the CCi, the tumor stage, and severe post-operative complications (Clavien-Dindo ≥3).

We have not found any description of the oncological protocol in the neoadjuvant or adjuvant settings. This aspect is important in the evaluation of oncological outcomes. In fact, the introduction of FOLFIRINOX regimen in adjuvant settings of resected PDAC has led to significantly longer survival rates compared to the use of the gemcitabine regimen, at the expense of a higher incidence of toxic effects. The FOLFIRINOX regimen as neoadjuvant treatment for borderline resectable and locally advanced PDAC had an increased rate of R0 and, consequently, it improved the survival rate (10,11). In Girgis *et al.*'s paper, we were not made aware if different types of chemotherapy agents were used between the two groups: this aspect could have altered the oncological results of robotic and open pancreatectomy.

Analyzing OS, no differences were found between the groups concerning 30- and 90-day post-operative mortality (2.2% and 4.8% *vs.* 1.3% and 4.4% respectively in open *vs.* robotic approach). In these settings, the predicting factors for better OS in the multivariate analysis were the robotic approach, the presence of R0 margin, the absence of metastatic LN, more than 6 cycles of adjuvant CHT and the reduction of severe post-operative complications (Clavien-Dindo ≥3). The authors speculate that the RP was a positive predicting factor to increase OS due to significant reduction of per-operative blood loss and transfusion.

In conclusion, this study showed encouraging results: the robotic approach seems to improve operative time, number of LN harvested, reduced blood loss and transfusion. Missing elements make it impossible to extrapolate a definitive conclusion: currently, it is still too early to affirm that the RP has the same long-term oncological results of open pancreatic surgery. We believe that a selection of patients, above all the absence of vascular contact, and a faithful reproduction of open approach steps in robotic field, are the keys factors to achieve similar oncological results between the two techniques. We think that in the absence of a RCT regarding the surgical aspects of robotic pancreaticoduodenectomy, we cannot compare oncological outcomes between robotic and open pancreatic surgery. We await the final results of the ongoing NCT04211948 trial (12).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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