Editorial

Is there a survival benefit of a robotic approach to pancreatoduodenectomy for pancreatic cancer?

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Comment on: Rosemurgy AS, Ross SB, Espeut A, *et al.* Survival and Robotic Approach for Pancreaticoduodenectomy: A Propensity Score-Match Study. J Am Coll Surg 2022;234:677-84.

Keywords: Pancreatic cancer; pancreatoduodenectomy; robotic surgery; survival; propensity score

Submitted Oct 21, 2022. Accepted for publication Dec 20, 2022. Published online Jan 11, 2023.
doi: 10.21037/hbsn-22-500
View this article at: https://dx.doi.org/10.21037/hbsn-22-500

Pancreatic cancer has an overall poor prognosis, and only about 15% can be offered surgical resection. Current systemic therapy can achieve median overall survival rates up to 54 months, as reported in the PRODIGE-24 trial, for those who complete resection, have good performance status, a low carbohydrate antigen (CA) 19-9 value and complete adjuvant therapy (1). Since many patients never reach adjuvant therapy after surgery, giving neoadjuvant therapy has become a favored approach even for resectable and borderline pancreatic cancer with a demonstrated survival benefit (2).

Parallel to the advances to the systemic oncological treatment, the surgical community has expressed an increasing interest in minimal-invasive access to pancreatic surgery. While minimal-invasive access has become the preferred approach for distal pancreatectomy, the role of minimal-invasive approach to a pancreatoduodenectomy is much less clear (3,4). Indeed, for the Whipple procedure (pancreatoduodenectomy), the overall benefits have been questioned, with a randomized trial (LEOPARD-2) of laparoscopic *vs.* open pancreatoduodenectomy terminated early due to increased mortality in the laparoscopic arm and with no difference in the time to recovery (5), as the primary outcome of the trial. Robotic pancreatoduodenectomy is believed to overcome some of the inherent technical challenges with laparoscopy, but randomized data are still lacking. However, data from expert, high-volume centers with a decade long experience in robotic or laparoscopic pancreatic surgery report similar outcomes to open resections, for both short-term and long-term results (6,7). Survival largely follows the pattern of histopathological subtypes (pancreatic cancers do worse compared to any other periampullary tumors) and stage (reflecting the biology of the disease) rather than mode of surgical access.

A bold conclusion in a recent paper by Rosemurgy *et al.* (8) thus warrants scrutiny. The authors present a major survival difference between patients having robotic and open pancreatoduodenectomy for pancreatic cancer, with 37 *vs.* 24 months survival favouring those who underwent robotic surgery. An even higher survival difference is reported in the propensity score matched (PSM) groups, with 41 months for robotic compared to only 17 months for open pancreatoduodenectomy. The survival difference, which they strongly argue to be an effect of the robotic approach,

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is unmatched in contemporary cancer therapy available for pancreatic cancer. Hence, the data, presentation, and analyses warrant careful considerations.

First, PSM may be considered for observational data in which an inherent selection bias is present, in an attempt to simulate randomization ('quasi-randomization') or at least narrow the selection bias between groups (9). In the study (8), only age, sex, and stage were used in the PSM; stage is a post hoc variable obtained only after final pathology is available. Of note, in their preferred institutionally preferred "surgery first" approach, neoadjuvant was given 3 times as often in the open surgery group compared to robotic (13% *vs.* 4%; P=0.04), and also for the adjusted PSM cohort (19% *vs.* 11%; P=0.24) despite not statistically significant. The reason for this was not declared but, most likely, represents more locally advanced tumor features in the open cohort, as this was not controlled for in the PSM groups (e.g., larger tumors; tumors closer to vessels; invasive patterns etc.). Also, before PSM there was a notably difference in tumor size between the open and robotic group as well as no information on functional status or comorbidities prior to surgery, which also are known features associated with survival outcomes. More importantly, the PSM did not include year of surgery; hence, the robotic cases done in the latter part of the period will be biased towards shorter follow up and, hence, fewer recurrences and reported deaths from cancer (less time at risk for recurrence). Furthermore, only 29% of the 521 patients where matched (8), hence a considerable selection bias in the results. On top of that, only one quarter of robotic cases could be matched to an open case. Thus, generalizability and robustness of the findings need to be questioned.

The study provides no information on follow-up time. We believe a classic error in interpretation of actual *vs.* actuarial survival has been done (10), an issue well known to produce inflated results after surgery for pancreatic cancer. Further, the number of patients completing adjuvant treatment after surgery was not reported. A shift in adjuvant treatment regimens has occurred towards more use of toxic but effective regimens (e.g., FOLFIRINOX). Indeed, a significant higher proportion of patients in the robotic group received FOLFIRINOX (29% *vs.* 6%, P=0.03). Surprisingly, this is not addressed as a possible explanation for the findings by the authors.

Improved survival after robotic pancreatoduodenectomy with PSM have to date never been reported in the current existing literature, regardless of type of cancer, to the best of our knowledge (4). Three other publications using PSM to investigate survival differences in robotic and open pancreatoduodenectomy, concluded with no difference in disease-free or overall survival (11-13). There is no difference in return to intended oncological therapy (RIOT) between open a minimal-invasive approach in population-based data from the USA (14), but one in every three patient (33%) does not receive adjuvant therapy after surgery (14)—a fact that is well documented to inferior survival.

With the abovementioned considerations, we suggest that the perception of a superiority in the robotic approach in regards to survival should be tempered, if not avoided altogether, as there are several methodological issues and limitations not accounted for in the study reported in *JACS* (8). The authors' bold claim that "*…robotic pancreaticoduodenectomy provides salutary and survival benefits for reasons yet unknown*" is hence unsubstantiated. At best, it represents a misunderstood scientific appreciation of data and methods used. At worst, it may represent promotion based on commercial interest and financial incentives. The authors promote a surgical practice based on robotic approach and have previously reported receiving honoraria from industry, not disclosed in said paper. Either way, until future well conducted randomized trials show a potential gain in survival by the robotic approach, such statements should be avoided.

In conclusion, we would respectfully suggest that the survival difference related to robotic surgery to be the result of lack of proper balance in other risk-factors between groups, as well as the inherent selection of cases, variation in adjuvant treatment and failure to control for observation time in the cohort, to mention some of the known unknowns. It is our belief that a gain in oncological survival is unlikely achievable based on mere surgical access. Surgical resection is a prerequisite for good oncological outcome, but rarely if ever achieves cure alone. The biology of pancreatic cancer needs to be better understood and multimodal treatment optimized beyond the surgeons' cure by cold steel, let alone the robotic arm as such.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-500/coif). The authors have no conflicts of interest to declare.

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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Cite this article as: Kleive D, Yaqub S, Søreide K. Is there a survival benefit of a robotic approach to pancreatoduodenectomy for pancreatic cancer? HepatoBiliary Surg Nutr 2023;12(1):92-94. doi: 10.21037/hbsn-22-500