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Editorial

EDITORIAL

Bias and Pancreatic Cancer Reporting

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In this issue of the Journal, Janssen et al. (1) publish the first results of the Trans-Atlantic Pancreatic Surgery consortium. In considering the assembly of data from selected institutions, a number of important issues related to potential for bias must be taken into account when interpreting the findings. First, the nature of the consortium itself—5 self-selected high-volume centers with multidisciplinary teams for treatment of pancreatic cancer—raises the question of bias. We do not know how or why these 3 US (Memorial Sloan Kettering [MSK], MD Anderson, and University of Pittsburgh) and 2 Dutch (Erasmus Medical Center Rotterdam and University of Amsterdam) institutions would decide to pool their data. The authors state that the institutions are all high-volume referral centers with broad expertise in the multidisciplinary management of patients with pancreatic cancer, particularly expertise in pancreatic surgery, and have similar approaches to patients with pancreatic cancer. However, these features are not unique to these institutions, and although they suggest the data set provides "real-world" experience, we suggest that a number of aspects of the consortium may introduce bias. Although the consortium may have initially been developed through networking and shared academic interests and the group represents highly accomplished and dedicated cancer centers, important differences between the institutions must be considered. Since 2005 there has been an effort at centralization of pancreatic surgery services in the Dutch health-care system, resulting in marked improvements in morbidity and survival (2). Regarding selection bias, we do know that both MSK and MD Anderson have a high proportion of patients who are self-referred and highly motivated. In addition, insurance considerations may affect those who are seen in these institutions. Janssen et al. (1) have not provided statistics by site and demographics on the diversity of the population or variance in diversity by site; however, we can assume these are skewed toward White European individuals. The number of minority patients in the Netherlands is low, and historically the same is true for MSK, whose results typically show underrepresentation of minority patients compared with the New York City area generally.

A number of other concerns regarding inherent bias exist. Regional differences in patient health may be a factor. Baseline body surface area (BSA) (found to be a prognostic factor here), given the known higher rates of metabolic syndrome in the US vs Netherlands, could have resulted in heterogeneity of results. There was no mechanism for central review of computed tomography scans used to judge if patients were resectable and whether to categorize as potentially resectable (PR), borderline resectable (BR), or locally advanced (LA), though the criteria for such categorization exist (e.g. National Comprehensive Cancer Network guidelines). In the experience of a recent SWOG trial for "resectable" pancreatic cancer, almost 40% of patients were not found to fit this category on central review, and prospective central review was initiated (Sohal, personal communication). Presumably, at these high-volume centers this kind of determination would be more consistent, but we have no idea of the concordance of these radiologists ranging from Rotterdam to Houston. Inherent biases in the application of radiation therapy for pancreatic cancer seems likely as well. The overall rate for radiation therapy in this database is 49%, running from 35% for PR to 58% for LA patients, but no criteria for radiation are stated and we do not know if it was more commonly used at some institutions vs others. And, most important, this data base is uncontrolled and retrospective. Although the authors suggest uniformity in approach, there was no protocol in place to guide consistency of dosing and dose modifications for the mFOLFIRINOX used, for timing of radiation and surgery, and for proceeding with surgical resection.

Nevertheless, the study provides important and credible information regarding short- and long-term outcomes in this clinical setting such as R0 resection rate and overall survival in the hands of practitioners at select high-volume referral centers. Of the 1835 patients included in the analysis, it is disconcerting that less than one-half (854 patients or 46.5%) ultimately underwent surgical exploration and only approximately one-third (695 or 37.8%) successfully underwent resection. This reflects the fact that approximately one-half of the cohort had LA pancreatic ductal adenocarcinoma based on the MD Anderson Cancer Center clinical classification system or the National Comprehensive Cancer Network criteria. The main differences between the 2 classification systems relate to the extent of mesenteric venous involvement. Resection rates were only 17.6%

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for patients with initially LA tumors, 53% for BR tumors, and approximately 70% for patients with PR tumors. Vascular reconstruction was performed in 42% of patients, and arterial resection and reconstruction was performed in almost 20% of patients, suggesting that these were generally complex procedures and outside the range of the standard "Whipple" or pancreatic body resection. However, 30- and 60-day postoperative mortality in this high-risk group was only 1% and 2%, respectively. Interestingly, R0 resection rates in this study were approximately 80% in PR patients and 63% in BR patients, which is lower than that previously reported by the first author of this study and others after neoadjuvant FOLFIRINOX with or without radiation therapy (3-5). Across the board, a pathologic complete response was observed in just over 5% of patients.

Radiotherapy was a component of treatment in almost one-half of the cohort, and this study does not address the role of radiotherapy in this patient population. However, the alluvial diagram [Figure 1B in (1)] does not seem to indicate a very large difference in resections for those with and without radiation. Several prospective cooperative group trials such as A021101 and A021501 will provide additional insights into the feasibility and potential clinical benefit of radiation in patients with BR or LA pancreatic cancer being treated with neoadjuvant FOLFIRINOX. In patients with LA pancreatic cancer, the low resection rate (17%) and overall poor survival (estimated median = 18 months) highlight the importance of continued clinical evaluation of radiation as an alternate to surgical resection. To that end, the similar outcomes associated with the use of hypofractionated ablative radiation in patients with LA pancreatic cancer are provocative and deserve continued evaluation (6).

Overall, despite the clear limitations of this consortium analysis (1), the large and broad nature of the retrospective experience gives us a sense of a large real-world experience in well-known cancer referral centers and most likely represents the most optimal estimate for results in nonclinical trial patients. Molecular studies attached to this data set may provide further insights into the nature of pancreatic cancer treatment. The reported estimates of the short-term and long-term endpoints and outcomes for patients with PR, BR, and LA pancreatic cancer treated with initial mFOLFIRINOX should help provide metrics for future trials. These data may also provide some credible benchmarks for real-world comparisons of outcomes in treating nonmetastatic pancreatic cancer.

If you are the type who listens to music while reading journals, consider that the most appropriate soundtrack for this article may be from Leonard Bernstein's *Candide*, "The Best of All Possible Worlds."

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Data Availability

No data were generated or presented in this editorial.

References

1. Janssen QP, van Dam JL, Doppenberg D, et al. FOLFIRINOX as initial treatment for localized pancreatic adenocarcinoma: a retrospective analysis by the Trans-Atlantic Pancreatic Surgery (TAPS) Consortium. *J Natl Cancer Inst*. 2022; 114(5):695–703.
2. Gooiker GA, Lemmens VEPP, Besselink MG, et al. Impact of centralization of pancreatic cancer surgery on resection rates and survival. *Br J Surg*. 2014; 101(8):1000–1005.
3. Janssen QP, Buettner S, Suker M, et al. Neoadjuvant FOLFIRINOX in patients with borderline resectable pancreatic cancer: a systematic review and patient-level meta-analysis. *J Natl Cancer Inst*. 2019;111(8):782–794.
4. Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: a phase 2 clinical trial. *JAMA Oncol*. 2018;4(7):963–969.
5. Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg*. 2015;261(1):12–17.
6. Reyngold M, O'Reilly EM, Varghese AM, et al. Association of ablative radiation therapy with survival among patients with inoperable pancreatic cancer. *JAMA Oncol*. 2021;7(5):735–738.