



Positive pancreatic neck margins—a telltale sign of complex biology

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Comment on: Zhang B, Lee GC, Qadan M, *et al.* Revision of Pancreatic Neck Margins Based on Intraoperative Frozen Section Analysis Is Associated With Improved Survival in Patients Undergoing Pancreatectomy for Ductal Adenocarcinoma. *Ann Surg* 2021;274:e134-42.

Submitted Dec 21, 2021. Accepted for publication Feb 15, 2022.

doi: 10.21037/hbsn-21-553

View this article at: <https://dx.doi.org/10.21037/hbsn-21-553>

Opinions remain divided on the definition, status and prognostic role of a positive pancreatic resection margin. The absence of a consensus definition for an R1 resection and the lack of a standard method to assess pancreatic resection specimens contribute to the ongoing controversy. These are some of the variables to consider when reviewing the literature on the role of resection margin status; a topic further complicated by the shifting landscape of pancreatic cancer management and the innate differences in institutional practices.

Recently, Zhang and colleagues from the Massachusetts General Hospital (MGH) and the Verona Pancreas Institute published their joint experience on revising pancreatic neck margins found to be positive on intraoperative frozen section (FS) analysis. This is a crucial area to explore because it addresses two interlinked debates, the role of intraoperative FS analysis and the benefit of extending resections to revise positive neck margins. In their retrospective review, titled “Revision of the Pancreatic Neck Margin Based on Intraoperative Frozen Section Analysis in Patients Undergoing Pancreatectomy for Ductal Adenocarcinoma”, the authors observed that extended resection, via re-resection of a positive neck margin or conversion to a total pancreatectomy, was not only safe to perform but was also associated with improved overall survival (OS) (1). Their promising conclusions, however, are best appreciated when interpreted in light of other similar institutional experiences.

Currently, there is no consensus definition for an R0 resection. The Union of International Cancer Control

defines an R0 resection by the absence of tumor cells along the transection line on microscopic evaluation (2) This is the definition Zhang and colleagues used. In another widely adopted definition, an R0 resection is defined by the absence of tumor cells within 1 mm of the transection line on microscopic evaluation (3,4). The use of different definitions makes it difficult to compare study results from different groups (5). Despite the different definitions, published data revealed that the survival benefit of an R0 resection was independent of the used definition (6), which suggests that better identification of R1 status is more crucial than which definition is superior.

Another challenge is standardizing the evaluation of pancreatic resection specimens and resection margins. Verbeke and colleagues outlined a standard protocol that evaluates resection specimens with a high degree of scrutiny. In their study, they described the six margins of a pancreaticoduodenectomy specimen, those being the anterior surface, the posterior and medial margins in contact with major abdominal vessels, the enteric margin, the bile duct margin and the pancreatic neck margin (3). They also described the circumferential resection margin and argued that a positive margin is defined by the presence of tumor cells within 1 mm of the closest margin (3). Interestingly, the rate of R1 resections increased as more specimens were evaluated using their standard protocol (3). Furthermore, many previously classified R0 resections were found to be R1 resections (3). More importantly, they observed that the most frequently involved margins were the posterior and medial margins whereas the pancreatic neck transection

surface was the least likely to be involved (3). Furthermore, a positive transection surface was not associated with other positive margins (7). Several other institutional experiences reported the same observation (3,4,6). In the experience of Zhang and colleagues, PV/SMA margins were positive in 13.9% of en-bloc resections (CR-EB), 18.2% of non-en-bloc resections (CR-NEB), and 18% in incomplete resections (IR Neck) (1).

This brings us to the heart of the matter, should we re-resect a positive neck margin based on frozen section analysis, and if so, how extensive should the re-resection be? If re-resection is technically feasible, most surgeons would consider it since it is the reason why they sent the margin for FS analysis in the first place. The decision to obtain a FS analysis is more nuanced since it is largely surgeon-dependent and is not a standard practice. The MGH and Verona experience reflects this, with FS analysis obtained in 79.6% of patients during the study duration (1). According to Pang and colleagues, intraoperative FS improved the rate of R0 resections but patients who underwent neck margin revision performed worse than their primary R0 and R1 counterparts (7). Mathur and colleagues concluded similarly (8). Although positive FS of the neck margin can help guide the decision to re-resect more pancreatic tissue, it does not address the posterior and medial vascular margins which cannot be revised in most cases without increasing the complication rates. The multi-institutional experience reported by Kooby and colleagues revealed that even when SMA margins were negative, revision of positive neck margins did not improve OS (5). This contrasts the work of Zhang and colleagues who concluded that revision of positive neck margins, a surgeon-modifiable factor, improved survival, irrespective of SMA margin status (1). The comparison may be limited by the different definitions used for R0 resections in both studies, however given the conclusion by Demir *et al.*, the comparison can be made with confidence.

The challenge goes beyond deciding whether to re-resect, but to how extensive the re-resection should be, whether to re-resect further after a persistently positive revised margin, and whether it is worthwhile to perform a total pancreatectomy to chase a negative margin. In the early experience of Schmidt and colleagues, patients with isolated positive neck margins who went on to receive a total pancreatectomy had improved OS compared to their R1 counterparts (9). Again, in the experience of Zhang and colleagues, 28.3% of patients in the CR-NEB group underwent a total pancreatectomy compared to

1.6% in the CR-EB group (1). As to the postoperative course of total pancreatectomy patients, the literature remains divided, with some reporting high postoperative morbidity and slower recovery, hence poorer tolerability to chemotherapy (10). More data are needed to study the impact of the postoperative course of these patients with total pancreatectomy on the overall survival.

There is a popular notion that a positive margin is a marker of more aggressive biology. Without including surgeon-modifiable factors, this notion is controversial. Margin status should be taken in the context of other disease-specific characteristics. In node negative disease, patients who received R1 resections fared worse than their R0 counterparts but this association was not observed in node positive disease (11). Furthermore, more positive margins meant worse OS (12), with the medial, or SMA, margin the most predictive of all (13). The survival benefits of adjuvant chemotherapy are appreciated independently of margin status (1,14). Furthermore, the impact of neoadjuvant chemotherapy is not widely commented on, in part because the majority of studies include older datasets (1,5,6,12). In surgically resected patients who received total neoadjuvant chemotherapy, the association of margin status and OS is no longer appreciated (15).

Overall, the work of Zhang and colleagues adds high-quality data to a long running debate. As any other great studies, more questions remained unanswered. With growing evidence supporting the survival benefit of R0 resections, the question becomes what can be done to improve the likelihood of an R0 resection for all margins. With more effective neoadjuvant chemotherapy as well as more aggressive management of locally advanced tumors, achieving a balance of negative margins and reduction of surgical morbidity is critical. Furthermore, the contested role of intraoperative FS analysis should be recontextualized to assist with intraoperative decision making, especially with improvements in intraoperative radiotherapy. All this should be balanced to achieve the best possible outcomes but not at the expense of added morbidity from achieving negative margins.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned

by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-553/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: Ghabi E, He J. Positive pancreatic neck margins—a telltale sign of complex biology. *HepatoBiliary Surg Nutr* 2022;11(2):302-304. doi: 10.21037/hbsn-21-553