Short Communication

The concept of 'borderline resectable' pancreatic cancer: limited foundations and limited future?

John A. Windsor[1,2], Savio George Barreto[3]

[1]HBP/Upper GI Unit, Department of General Surgery, Auckland City Hospital, Auckland, New Zealand; [2]Department of Surgery, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand; [3]Hepatobiliary and Oesophagogastric Unit, Division of Surgery and Perioperative Medicine, Flinders Medical Centre, Bedford Park, Adelaide, South Australia, Australia

Correspondence to: John A. Windsor. Professor of Surgery, Department of Surgery, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand. Email: j.windsor@auckland.ac.nz.

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is traditionally treated by a surgery-first approach. The development and adoption of the concept of borderline resectable PDAC, which extends the role of surgery, is based on the proposition that neoadjuvant therapy (NAT) will increase the resection rate, margin negative rate and overall survival. There are a number of issues with this concept and a critical review of these suggests that it is based on limited foundations and likely has a limited future.

Keywords: Morbidity; survival; mortality; outcomes; research

Submitted Aug 22, 2016. Accepted for publication Oct 10, 2016.
doi: 10.21037/jgo.2016.12.06
View this article at: http://dx.doi.org/10.21037/jgo.2016.12.06

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis. The nihilism surrounding PDAC (1), the deadliest of solid cancers, is based on overall survival data that remain rooted in single digits. The best chance of survival is by surgical resection (2,3) although the chilling reality is that a curative surgical resection (i.e., negative margins or R0) is only possible in a fifth of patients of whom only 20% are alive at 5 years (4). Despite this, a surgery-first approach remains the cornerstone of curative treatment for only a minority of patients with resectable disease because resection has become more safe (5) and effective systemic treatments are still awaited (6). It is no surprise that in the drive to achieve better results some surgeons advocate more radical surgery to treat more patients (7-9). This drive has helped spawn the concept of 'borderline resectable' disease, first proposed 15 years ago (10). The rationale is easy to follow. If patients are likely to be left with residual cancer after resection and if they can be identified before resection it might be possible to down stage the disease by neoadjuvant therapy (NAT). The advantages of this approach are that a higher proportion of patients receive multimodality therapy (11), there is an increase in resection rate (12), negative margin rate (13) and overall survival. This approach also allows time for occult systemic cancer to become evident, during the course of NAT, and thus avoiding futile surgery.

There are several issues with the concept of 'borderline resectable' PDAC (BR-PDAC) and a critical examination of these calls into question the long-term viability of the concept.

Almost all patients have systemic disease when they present with PDAC

It has been calculated that over a decade is required for localised PDAC to develop subclones with metastatic potential, but at the time patients present for treatment the vast majority already have systemic disease (14). This is supported by histopathology examination of early PDAC where perineural and/or lymphovascular invasion is ubiquitous indicating a marked propensity for systemic spread at the time of treatment. This goes some way to explaining the finding that 85% of patient having a 'curative resection' succumb with systemic metastases (15,16). Other evidence that pancreatic cancer might be metastatic from the time patients present

© Journal of Gastrointestinal Oncology. All rights reserved.

comes from computer modelling (17) and experimental mouse models (18). While exceptions exist, for the majority of patients the 'horse has bolted' by the time they present, as treated or untreated they will die with systemic disease (16). The importance of this is that despite radical surgical resection the outcome will usually be determined by pre-existing systemic disease and whether it responds to NAT, and not the radicality of surgery.

The decision to give NAT requires accurate identification of BR-PDAC

The ability to establish whether it is possible to improve survival by treating BR-PDAC with NAT has been hampered by the 'imprecise continuum between radiologically and technically resectable and unresectable disease' (19). There are no less than seven different published definitions of BR-PDAC (20) all of which use ambiguous terms (e.g., abutment, impingement, narrowing, encasement, invasion, and adherence) and an arbitrarily determined measurement (e.g., ≥180° of circumference). Interpreting and comparing studies of NAT for BR-PDAC is difficult because they use these different definitions, chemotherapy and radiation therapy protocols and are typically small retrospective studies. Even if proponents of the BR-PDAC concept achieve consensus on accurate definitions, the prognostic relevance of the elements and reliability of their interpretation still need to be determined.

The selection of patients with BR-PDAC for NAT relies on anatomic criteria, which are not 'fit for task'

The various definitions of BR-PDAC are based on the relationship of computed tomography (CT)-detectable tumour to adjacent vessels. The problem is that the anatomic extent of tumour is often difficult to determine and the extent does not indicate the aggressiveness of the tumour, the likelihood of systemic metastases, or responsiveness to NAT. This is not to say that anatomic elements do not have some prognostic significance, but that they are not sufficient for selecting patients. It is known, for instance, that there is a worse outcome if more than 3 cm of the portal/superior mesenteric vein is involved (21,22) and if there is microscopic invasion through to the intima of the vein (23). Staging CT scanning can identify the former, but not the latter. A fresh approach to pre-operative staging is needed to provide criteria that will advance our decision-making, allow tailoring of treatment and permit more accurate prediction of outcome. In short, we need biologic and not anatomic criteria to select patients. It has been suggested that different patterns of failure in PDAC indicate distinct morphological and genetic subtypes with different patterns of metastases (24). For instance, an intact SMAD4/DPC4 gene might be used to select patients for pancreatic resection (25) as this is associated with a lower risk of distant metastases (24). Recently an integrated genomic expression analysis of 456 PDACs convincingly demonstrated that PDAC represents four distinct subtypes; squamous, pancreatic progenitor aberrantly differentiated endocrine exocrine (ADEX) and immunogenic types (26). The future of preoperative staging will involve pre-treatment tumour sampling and targeted genomic analysis to allow accurate selection of patients for tailored treatments. When this occurs the importance of anatomic criteria will rapidly fade.

It is not known if NAT improves the negative margin rate after resection

The justification for giving NAT to patients with BR-PDAC is not only to treat occult systemic disease, but also to reduce the risk of a positive resection margin (27). Confirming the latter is problematic because the risk of a positive margin in patients with BR-PDAC who do not receive NAT has not been determined. Thus the actual contribution of NAT to reducing the risk of a positive margin is not known because the available evidence is of low level and conflicting. A systematic review found that the R0 resection rates between tumours considered resectable and unresectable before NAT were not different after resection (82.1% *vs.* 79.2%) (28). This suggests that NAT did not increase the negative margin rate after resection. There is other evidence suggesting the reverse, that neoadjuvant combined therapy leads to a higher negative resection margin rate (13,29), which suggests that the addition of radiotherapy is essential to achieve a reduced R0 rate. While the objective of NAT is down-staging, the reality is that more often the effect is one of down-sizing, and this occurs in less than a third of patients (30). Neoadjuvant FOLFIRINOX has shown some promise with down-staging (31), but it is too toxic for many elderly patients. The ALLIANCE trial (32) has tested neoadjuvant chemotherapy followed by radiation therapy and failed to demonstrate an improvement in resection rates. Whether NAT increases the negative margin rate remains to be established.

© Journal of Gastrointestinal Oncology. All rights reserved.

It is not known if NAT improves overall outcome in patients with BR-PDAC who are resected

The ultimate proof for the concept of BR-PDAC would be to demonstrate that NAT improves overall survival. Evidence for this is not available as there have been no randomised clinical trials designed to test whether NAT in patients with BR-PDAC (or those with resectable disease, for that matter) improves overall survival (29,33). Lower levels of evidence suggest that combination NAT does not improve disease-free or overall survival (13). Therefore this question remains wide open. Whether the widespread adoption of the concept of BR-PDAC has effectively destroyed the practical equipoise necessary to conduct such trials (32) is untested. Any perceived survival advantage from NAT in patients with BR-PDAC, when compared with those with unresectable disease, might be due to other factors, including the latter harbouring more advanced stage disease, a higher incidence of preoperative arterial involvement and intraoperative incidental metastasis (34). While the primary question remains unanswered, there are considerable efforts being made to answer secondary questions such as which combinations of chemotherapy are most effective and whether radiotherapy should be included. Surely our best efforts should be directed towards determining whether NAT confers any survival advantage (35).

Accurate re-staging of BR-PDAC after NAT is not possible

Images from re-staging CT scans after NAT are difficult to interpret (36), because it is not possible to distinguish residual tumour, scarring from tumour regression, tumour desmoplasia, or inflammatory changes from NAT itself. This difficulty in accurately selecting which patients should proceed with resection means that the *a priori* decision for NAT almost inevitably commits a patient with BR-PDAC to a trial dissection after NAT, providing distant metastases do not arise in the interim. This almost certainly results in an increased proportion of patients undergoing trial dissection and synchronous vein resection (36), and probably without a reduction in the R1/R2 rate (37). Whether it is possible to more accurately stage the margins of concern with endosonography and fine needle aspiration for cytology remains to be seen (38). Whether adjunctive techniques such as 'margin accentuation' by irreversible electroporation can increase the R0 rate in this setting also remains to be seen (39,40). The inability to accurately re-stage patients with BR-PDAC after NAT remains an unsolved problem.

If NAT is indicated for patients with BR-PDAC, why is it not indicated for all those with PDAC?

The benefits of NAT, in terms of improved R0 rates and survival, might be more readily demonstrated in patients with resectable PDAC than BR-PDAC. Given the propensity for systemic spread in all patients with PDAC, the logical question is whether it should be indicated for all patients with PDAC (41). This question was vociferously debated over breast cancer many years ago. The Halsted concept of the primacy of radical local surgery, which probably retarded progress for almost a century, was successfully challenged by the Fisher concept of systemic therapy (42), using randomised controlled trials to demonstrate the importance of NAT. A similar revolution appears to be occurring in some centres that are now offering NAT for T1 and T2 PDAC. It is time to acknowledge that PDAC, even more than breast cancer, is a systemic disease at the time of presentation and that restricting NAT to a subgroup of patients (i.e., BR-PDAC) denies potential benefits for patients with resectable disease. Over-reliance on a surgery-first approach for PDAC has retarded progress. The reality is that surgery and even more radical surgery, though well intentioned, has not yielded acceptable results (9,37). And while we can be pleased that there has been a significant decrease in pancreatoduodenectomy-related morbidity and mortality over the last 3 decades (5), the efficacy of surgical treatment has reached its ceiling (5).

The foundations on which the concept of BR-PDAC has been proposed, developed and implemented are not strong. While extending the role of surgery to encompass a subgroup of patients with BR-PDAC who are down-staged by NAT has considerable appeal, the evidence to support this approach is relatively sparse. The reality is that despite our advances in staging, NAT and surgery there has been little impact on survival.

The future treatment of PDAC will be very different. NAT will become the standard of care for all patients with PDAC and will be tailored and targeted to subgroups of patients based on genomic analysis of their tumour. Patients at low risk of systemic metastases will be offered resection after NAT to confirm tumour kill and remove any residual viable cancer. Patients at high risk of systemic metastases

© Journal of Gastrointestinal Oncology. All rights reserved.

may not be offered surgical resection at all. While the concept of BR-PDAC has raised awareness about the importance of NAT for PDAC, the limited foundations and remaining issues suggest that it has a limited future.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Gudjonsson B. Pancreatic cancer. The need for critical reassessment. J Clin Gastroenterol 1996;23:2-6.
2. Janes RH Jr, Niederhuber JE, Chmiel JS, et al. National patterns of care for pancreatic cancer. Results of a survey by the Commission on Cancer. Ann Surg 1996;223:261-72.
3. Sener SF, Fremgen A, Menck HR, et al. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. J Am Coll Surg 1999;189:1-7.
4. Barugola G, Partelli S, Marcucci S, et al. Resectable pancreatic cancer: who really benefits from resection? Ann Surg Oncol 2009;16:3316-22.
5. Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg 2006;10:1199-210; discussion 1210-1.
6. Spadi R, Brusa F, Ponzetti A, et al. Current therapeutic strategies for advanced pancreatic cancer: A review for clinicians. World J Clin Oncol 2016;7:27-43.
7. Naganuma T, Isaji S, Kawarada Y. Staging and extended resection for pancreatic cancer. Pancreas 1998;16:355-62.
8. Sasson AR, Hoffman JP, Ross EA, et al. En bloc resection for locally advanced cancer of the pancreas: is it worthwhile? J Gastrointest Surg 2002;6:147-57; discussion 157-8.
9. Mollberg N, Rahbari NN, Koch M, et al. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. Ann Surg 2011;254:882-93.
10. Maurer CA, Zgraggen K, Büchler MW. Pancreatic carcinoma. Optimizing therapy by adjuvant and neoadjuvant therapy? Zentralbl Chir 1999;124:401-7.
11. Tzeng CW, Tran Cao HS, Lee JE, et al. Treatment sequencing for resectable pancreatic cancer: influence of early metastases and surgical complications on multimodality therapy completion and survival. J Gastrointest Surg 2014;18:16-24; discussion 24-5.
12. Bittoni A, Santoni M, Lanese A, et al. Neoadjuvant therapy in pancreatic cancer: an emerging strategy. Gastroenterol Res Pract 2014;2014:183852.
13. Pingpank JF, Hoffman JP, Ross EA, et al. Effect of preoperative chemoradiotherapy on surgical margin status of resected adenocarcinoma of the head of the pancreas. J Gastrointest Surg 2001;5:121-30.
14. Yachida S, Jones S, Bozic I, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 2010;467:1114-7.
15. Sohal DP, Walsh RM, Ramanathan RK, et al. Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy. J Natl Cancer Inst 2014;106:dju011.
16. Heestand GM, Murphy JD, Lowy AM. Approach to patients with pancreatic cancer without detectable metastases. J Clin Oncol 2015;33:1770-8.
17. Haeno H, Gonen M, Davis MB, et al. Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies. Cell 2012;148:362-75.
18. Rhim AD, Mirek ET, Aiello NM, et al. EMT and dissemination precede pancreatic tumor formation. Cell 2012;148:349-61.
19. Katz MH, Pisters PW, Evans DB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg 2008;206:833-46; discussion 846-8.
20. Barreto SG, Windsor JA. Justifying vein resection with pancreatoduodenectomy. Lancet Oncol 2016;17:e118-24.
21. Kaneoka Y, Yamaguchi A, Isogai M. Portal or superior mesenteric vein resection for pancreatic head adenocarcinoma: prognostic value of the length of venous resection. Surgery 2009;145:417-25.
22. Pan G, Xie KL, Wu H. Vascular resection in pancreatic adenocarcinoma with portal or superior mesenteric vein invasion. World J Gastroenterol 2013;19:8740-4.
23. Han SS, Park SJ, Kim SH, et al. Clinical significance of portal-superior mesenteric vein resection in pancreatoduodenectomy for pancreatic head cancer. Pancreas 2012;41:102-6.
24. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol 2009;27:1806-13.

© Journal of Gastrointestinal Oncology. All rights reserved.

25. Hruban RH, Adsay NV. Molecular classification of neoplasms of the pancreas. Hum Pathol 2009;40:612-23.
26. Bailey P, Chang DK, Nones K, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature 2016;531:47-52.
27. Heinemann V, Haas M, Boeck S. Neoadjuvant treatment of borderline resectable and non-resectable pancreatic cancer. Ann Oncol 2013;24:2484-92.
28. Gillen S, Schuster T, Meyer Zum Büschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 2010;7:e1000267.
29. McClaine RJ, Lowy AM, Sussman JJ, et al. Neoadjuvant therapy may lead to successful surgical resection and improved survival in patients with borderline resectable pancreatic cancer. HPB (Oxford) 2010;12:73-9.
30. Festa V, Andriulli A, Valvano MR, et al. Neoadjuvant chemo-radiotherapy for patients with borderline resectable pancreatic cancer: a meta-analytical evaluation of prospective studies. JOP 2013;14:618-25.
31. Petrelli F, Coinu A, Borgonovo K, et al. FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. Pancreas 2015;44:515-21.
32. Varadhachary GR, Fleming JB, Crane CH, et al. Phase II study of preoperation mFOLFIRINOX and chemoradiation for high-risk resectable and borderline resectable pancreatic adenocarcinoma. J Clin Oncol 2015;33:abstr 362.
33. Barugola G, Partelli S, Crippa S, et al. Outcomes after resection of locally advanced or borderline resectable pancreatic cancer after neoadjuvant therapy. Am J Surg 2012;203:132-9.
34. Kato H, Usui M, Isaji S, et al. Clinical features and treatment outcome of borderline resectable pancreatic head/body cancer: a multi-institutional survey by the Japanese Society of Pancreatic Surgery. J Hepatobiliary Pancreat Sci 2013;20:601-10.
35. Barreto SG, Windsor JA. Justifying vein resection with pancreatoduodenectomy - Author's reply. Lancet Oncol 2016;17:e178.
36. Katz MH, Fleming JB, Bhosale P, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. Cancer 2012;118:5749-56.
37. Giovinazzo F, Turri G, Katz MH, et al. Meta-analysis of benefits of portal-superior mesenteric vein resection in pancreatic resection for ductal adenocarcinoma. Br J Surg 2016;103:179-91.
38. Lee J, Tamm E. Pancreatic Carcinoma: Detection and staging. In: Bhutani M, Deutsch J. editors. EUS Pathology with Digital Anatomy Correlation: Textbook and Atlas. Shelton, Connecticut: People's Medical Publishing House, 2010:149-63.
39. Martin RC 2nd, Kwon D, Chalikonda S, et al. Treatment of 200 locally advanced (stage III) pancreatic adenocarcinoma patients with irreversible electroporation: safety and efficacy. Ann Surg 2015;262:486-94; discussion 492-4.
40. Kwon D, McFarland K, Velanovich V, et al. Borderline and locally advanced pancreatic adenocarcinoma margin accentuation with intraoperative irreversible electroporation. Surgery 2014;156:910-20.
41. Crippa S, Reni M, Balzano G, et al. Justifying vein resection with pancreatoduodenectomy. Lancet Oncol 2016;17:e177-8.
42. Fisher B. Laboratory and clinical research in breast cancer--a personal adventure: the David A. Karnofsky memorial lecture. Cancer Res 1980;40:3863-74.

Cite this article as: Windsor JA, Barreto SG. The concept of 'borderline resectable' pancreatic cancer: limited foundations and limited future? J Gastrointest Oncol 2017;8(1):189-193. doi: 10.21037/jgo.2016.12.06

© Journal of Gastrointestinal Oncology. All rights reserved.