Pancreatology 19 (2019) 204–205

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Is it time to reconsider the principles of pancreatic cancer surgery?

Keywords:
Survival
Pancreas
Outcomes
Radiation
Chemotherapy
Genetics

The past few decades have witnessed tremendous improvements in outcomes for surgery of the pancreas possibly linked to technical refinements, standardisation of practice, and service reconfigurations [1–3], amongst others. However, the overall survival of pancreatic cancer remains dismal [4] owing to the fact that pancreatic cancer patients more often, than not, present with unresectable or metastatic disease [5]. With the looming threat of it soon becoming the second leading cause for cancer-related mortality [6], the race to clarify pancreatic carcinogenesis continues to heat up.

Building on the existing pancreatic carcinogenesis progression model proposed in 2000 [7], Makohon-Moore and colleagues [8] recently demonstrated that independent, high-grade pancreatic precursor lesions observed in a single pancreas often represent a single neoplasm that has colonized the ductal system, accumulating spatial and genetic divergence over time. This elaborate and thorough body of work attests to the commitment of the investigators to unearthing the development of pancreatic cancer. The authors infer at the end of the study that this pathway could explain the high risk of recurrence in patients undergoing surgical resections for high-grade PanINs (pancreatic intraepithelial neoplasia) and pancreatic ductal adenocarcinoma based on their findings in 50% (4 out of 8) patients. However, from a clinical perspective, the study begs the question, 'is this pathway truly a significant cause for recurrent pancreatic cancer following surgical resection?' If this is so, then it will render current principles of surgical resection redundant making total pancreatectomy the only option for pancreatic cancer.

To explore this further, it must be clarified that for this pathway to be clinically relevant, the only acceptable form of locally recurrent pancreatic cancer should be disease within the remnant pancreas away from the resection margin and the pancreatic bed. The rationale for the latter assumption is that the vast majority of resections for pancreatic head cancer are R1 resections [9] – a known cause for local recurrence [10] at the aforementioned sites [11]. A thorough search of the published literature was carried out focussing on patterns of local recurrence after a complete, margin negative (R0) resection as this would provide the necessary data. Three studies provided the necessary information. Miyazaki and colleagues (6/326) [12] and Hashimoto and colleagues (6/339) [13] noted the incidence to vary between 1.7 and 1.8%. In another study, Comito et al. [14] reported 3 patients with recurrent disease in the remnant but failed to provide the total number of patients surgically resected within the study period.

We can thus conclude that the pathway of carcinogenesis proposed by Makohon-Moore and colleagues [8] is certainly valid. However, it does not represent a pathway sufficiently relevant from a clinical context to justify a change in current surgical practice. The likelihood that pancreatic cancer is a systemic disease at the time most patients present for treatment [15] even in the absence of radiologically discernible metastatic disease has been suggested by data from computer modelling [16], experimental mouse models [17], and histopathological evidence of the ubiquitous presence of perineural and/or lymphovascular invasion in early cancer specimens and supported by the finding that 85% of patient having a 'curative resection' succumb with systemic metastases [18,19]. Quite honestly, there remains a lot more that needs to be known about pancreatic cancer and its pathogenesis. However, until then, we must use the information that is already available to us to guide therapy. Given the recent data to support chromothripsis as a cause for the aggressive nature of pancreatic cancer [20], minimal genetic heterogeneity in metastatic disease [21], and encouraging results from large databases [22], it is imperative that we start to consider the role of perioperative chemotherapy not only in Borderline resectable, but even in resectable pancreatic cancer [23] (albeit within the confines of clinical trials [24]) – the only cohort of patients with the disease in whom we have an opportunity to alter outcomes for the better.

Acknowledgement

Nil.

Conflicts of interest

None to declare.

Role of funding source

Not applicable.

Ethics committee approval

Not applicable.

https://doi.org/10.1016/j.pan.2018.12.003

References

[1] Shrikhande S, Barreto S, Somashekar B, Suradkar K, Shetty G, Talole S, et al. Evolution of pancreatoduodenectomy in a tertiary cancer centre in India: improved results from service reconfiguration. Pancreatology 2013 Jan-Feb;13(1):63–71.

[2] Shrikhande SV, Barreto G, Shukla PJ. Pancreatic fistula after pancreaticoduodenectomy: the impact of a standardized technique of pancreaticojejunostomy. Langenbeck's Arch Surg 2008;393:87–91.

[3] Howard TJ, Krug JE, Yu J, Zyromski NJ, Schmidt CM, Jacobson LE, et al. A margin-negative r0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. J Gastrointest Surg 2006;10:1338–45. discussion 1345-1336.

[4] Nienhuijs SW, van den Akker SA, de Vries E, de Hingh IH, Visser O, Lemmens VE. Nationwide improvement of only short-term survival after resection for pancreatic cancer in The Netherlands. Pancreas 2012;41:1063–6.

[5] Barreto S, Windsor J. Justifying vein resection with pancreatoduodenectomy. Lancet Oncol 2016;17:e118–24.

[6] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913–21.

[7] Hruban RH, Goggins M, Parsons J, Kern SE. Progression model for pancreatic cancer. Clin Canc Res 2000;6:2969–72.

[8] Makohon-Moore AP, Matsukuma K, Zhang M, Reiter JG, Gerold JM, Jiao Y, et al. Precancerous neoplastic cells can move through the pancreatic ductal system. Nature 2018;561:201–5.

[9] Verbeke CS, Gladhaug IP. Resection margin involvement and tumour origin in pancreatic head cancer. Br J Surg 2012;99:1036–49.

[10] Ghaneh P, Kleeff J, Halloran CM, Raraty M, Jackson R, Melling J, et al. The impact of positive resection margins on survival and recurrence following resection and adjuvant chemotherapy for pancreatic ductal adenocarcinoma. Ann Surg 2017.

[11] Iacobuzio-Donahue CA, Fu B, Yachida S, Luo M, Abe H, Henderson CM, 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.

[12] Miyazaki M, Yoshitomi H, Shimizu H, Ohtsuka M, Yoshidome H, Furukawa K, et al. Repeat pancreatectomy for pancreatic ductal cancer recurrence in the remnant pancreas after initial pancreatectomy: is it worthwhile? Surgery 2014;155:58–66.

[13] Hashimoto D, Chikamoto A, Ohmuraya M, Sakata K, Miyake K, Kuroki H, et al. Pancreatic cancer in the remnant pancreas following primary pancreatic resection. Surg Today 2014;44:1313–20.

[14] Comito T, Cozzi L, Zerbi A, Franzese C, Clerici E, Tozzi A, et al. Clinical results of stereotactic body radiotherapy (sbrt) in the treatment of isolated local recurrence of pancreatic cancer after r0 surgery: a retrospective study. Eur J Surg Oncol 2017;43:735–42.

[15] Windsor JA, Barreto SG. The concept of 'borderline resectable' pancreatic cancer: limited foundations and limited future? J Gastrointest Oncol 2017;8:189–93.

[16] Haeno H, Gonen M, Davis MB, Herman JM, Iacobuzio-Donahue CA, Michor F. Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies. Cell 2012;148:362–75.

[17] Rhim AD, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, et al. Emt and dissemination precede pancreatic tumor formation. Cell 2012;148:349–61.

[18] Sohal DP, Walsh RM, Ramanathan RK, Khorana AA. Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy. J Natl Cancer Inst 2014;106:dju011.

[19] Heestand GM, Murphy JD, Lowy AM. Approach to patients with pancreatic cancer without detectable metastases. J Clin Oncol 2015;33:1770–8.

[20] Notta F, Chan-Seng-Yue M, Lemire M, Li Y, Wilson GW, Connor AA, et al. A renewed model of pancreatic cancer evolution based on genomic rearrangement patterns. Nature 2016;538:378–82.

[21] Reiter JG, Makohon-Moore AP, Gerold JM, Heyde A, Attiyeh MA, Kohutek ZA, et al. Minimal functional driver gene heterogeneity among untreated metastases. Science 2018;361:1033–7.

[22] Hashmi A, Kozick Z, Fluck M, Hunsinger MA, Wild J, Arora TK, et al. Neoadjuvant versus adjuvant chemotherapy for resectable pancreatic adenocarcinoma: a national cancer database analysis. Am Surg 2018;84:1439–45.

[23] Barreto SG, Windsor JA. Justifying vein resection with pancreatoduodenectomy - author's reply. Lancet Oncol 2016;17:e178.

[24] O'Reilly D, Fou L, Hasler E, Hawkins J, O'Connell S, Pelone F, et al. Diagnosis and management of pancreatic cancer in adults: a summary of guidelines from the UK national institute for health and care excellence. Pancreatology 2018.

Savio G. Barreto*

Division of Surgery and Perioperative Medicine, Flinders Medical Centre, Bedford Park, Adelaide, South Australia, Australia

College of Medicine and Public Health, Flinders University, South Australia, Australia

Bhawna Sirohi

Department of Medical Oncology, Barts Cancer Institute, Queen Mary University of London, London, UK

* Corresponding author. Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia, 5042, Australia.
E-mail addresses: georgebarreto@yahoo.com, savio.barreto@sa.gov.au (S.G. Barreto).

12 October 2018
Available online 8 December 2018