Refining the care of patients with pancreatic cancer: the AGITG Pancreatic Cancer Workshop consensus

"The treatment of operable pancreatic cancer is entering a new phase of multimodal therapy"

Robert C Gandy MB ChB, MS, FRACS[1]

Andrew P Barbour MB BS, PhD, FRACS[2]

Jaswinder Samra DPhil, FRCS(Eng), FRACS[3]

Mehrdad Nikfarjam MB BS, FRACS, PhD[4]

Koroush Haghighi MB BS, FRACS[1]

James G Kench MB BS, FRCPA[5]

Payal Saxena FRACS, PhD[5]

David Goldstein MB BS, FRCP[UK], FRACP[1,6]

1 Prince of Wales Hospital, Sydney, NSW.
2 University of Queensland, Brisbane, QLD.
3 Royal North Shore Hospital, Sydney, NSW.
4 Austin Health, Melbourne, VIC.
5 Royal Prince Alfred Hospital, Sydney, NSW.
6 UNSW Prince of Wales Clinical School, Sydney, NSW.

d.goldstein@unsw.edu.au

doi: 10.5694/mja16.00061

Pancreatic adenocarcinoma is the 11th most frequent cancer in Australia.[1] The disease has a poor prognosis: the overall 5-year survival rate is about 4%, and 5-year survival in those who are eligible for surgery is 20–21%,[2] which is significantly better than the 5-year survival rate of 3% for people with metastatic disease. Internationally, about 20% of patients have potentially resectable disease after staging; there is currently no strategy for early detection. Recent Australian data indicate that about 15% of patients with pancreatic adenocarcinoma undergo surgery.[3]

Modern imaging techniques have improved diagnostic precision, especially in differentiating adenocarcinoma from non-malignant pancreatic masses (pseudo-cyst, lymphoma, chronic pancreatitis, intraductal papillary mucinous neoplasms, neuroendocrine tumours). Important prognostic indicators for long term patient survival include negative or tumour-free surgical margins, as well as tumour size, lymph node status, and the absence of metastases.[4-6] Margins, number of lymph nodes identified (and examined) and accurate determination of tumour size are influenced by the quality of surgery and the surgical definitions used. The lack of widely accepted clear and precise definitions of surgical margins, surgical procedures and pre-operative resectability has contributed to significant variability in 5-year survival rates and local control, and hampers efforts to define the role of adjuvant therapy in treating pancreatic cancer.

Post-operative adjuvant therapy can improve survival,[2] but the ability of patients to safely receive chemotherapy after pancreatic surgery is compromised by their slow recovery and the consequences of surgical morbidity. As many as 25% of patients never receive the indicated treatment, and, even with treatment, local recurrence at distant sites is frequent.[2] A new approach to improving outcomes is the increasing use of pre-operative adjuvant therapy, which has advantages over post-operative treatment in terms of lower toxicity and improved tolerability, because the patients are usually fitter and less nutritionally compromised. These advantages have been observed in the treatment of selected breast, oesophageal, gastric and rectal cancers. Neo-adjuvant therapy may have three benefits: increasing the proportion of patients receiving systemic therapy; identifying early disease progression before a potentially debilitating surgical procedure without associated benefit; and possible tumour shrinkage (downstaging).

The Australasian Gastro-Intestinal Trials Group (AGITG), in partnership with the Avner Nahmani Pancreatic Cancer Foundation, convened the Australasian Pancreatic Cancer Workshop in July 2015.[7] The primary aims of this expert panel of health professionals and consumers — including medical and radiation oncologists, surgical subspecialists, anatomical pathologists, gastroenterologists, and nursing and allied health professionals — were to develop a consensus statement on the operability of pancreatic cancer and the role of neo-adjuvant therapy in enhancing the benefits of surgery. The discussion below represents an agreed optimal approach to the key aspects of surgical management.

Summary

- A meeting of the Australasian Gastro-Intestinal Trials Group (AGITG) was held to develop a consensus statement defining when a patient with pancreatic cancer has disease that is clearly operable, is borderline, or is locally advanced/inoperable.
- Key issues included the need for multidisciplinary team consensus for all patients considered for surgical resection. Staging investigations, to be completed within 4 weeks of presentation, should include pancreatic protocol computed tomography, endoscopic ultrasound, and, when possible, biopsy.
- Given marked differences in outcomes, the operability of tumours should be clearly identified by categories: those clearly resectable by standard means (group 1a), those requiring vascular resection but which are clearly operable (group 1b), and those of borderline operability requiring vascular resection (groups 2a and 2b). Patients who may require vascular reconstruction should be referred, before exploration, to a specialist unit.
- All patients should have a structured pathology report with standardised reporting of all seven surgical margins, which identifies an R0 (no tumour cells within a defined distance of the margin) if all surgical margins are clear from 1 mm.
- Neo-adjuvant therapy is increasingly recommended for borderline operable disease, while chemotherapy is recommended as initial therapy for patients with unresectable loco-regional pancreatic cancer. The value of adding radiation after initial chemotherapy remains uncertain. A small number of patients may be downstaged by chemoradiation, and trimodality therapy should only be considered as part of a clinical trial.
- Instituting these recommendations nationally will be an integral part of the process of improving quality of care and reducing geographic variation between centres in outcomes for patients.

Staging

The accurate staging of pancreatic cancer prior to surgery guides appropriate and individualised treatment of

patients. The detection of advanced disease at diagnosis may prevent unnecessary, morbid surgery. In addition, the ability to precisely describe the relationship of the tumour to the surrounding vasculature influences consideration of the appropriate procedure and the risk of a positive surgical margin, and accordingly influences decisions about pre-operative chemotherapy or considering a clinical trial.

Imaging

Modern computed tomography (CT) allows high definition imaging of the primary lesion and its relationship to the vascular anatomy of the pancreas,[8] as well as assessment of the regional and non-regional lymph nodes and potential sites of metastases. The minimum requirement for radiological staging is consequently a pancreatic protocol CT scan of the chest, abdomen and pelvis. Standardised reporting templates have been shown to improve decision making and to facilitate clinical trials.[9] The accuracy of CT is lower for small or cystic lesions of the pancreas, for which magnetic resonance imaging (MRI) may provide better delineation. MRI is also superior for assessing small liver lesions when metastases need to be excluded. Endoscopic ultrasound (EUS) is useful for diagnosing small lesions not visible on cross-sectional imaging, and is a good adjunct to CT in local staging. ^{18}F-Fluorodeoxyglucose positron emission topography/computed tomography (FDG PET/CT) may significantly alter treatment intention in a small group of patients and may prevent unnecessary laparotomy.[10]

Biopsy

Endoscopic ultrasound is the preferred method for tissue and fluid acquisition (primary and lymph node), as there is a low sampling error and reduced risk of peritoneal soiling.[11] EUS-guided fine needle and core biopsy, especially when an on-site cytopathologist is available, has greatly improved accuracy and allows for the molecular profiling of tumours.[12] Biopsy is preferred but not mandatory for all patients, despite a 2% risk of pancreatitis. However, biopsy is mandatory prior to neo-adjuvant and palliative therapy (to exclude alternative diagnoses for which another systemic therapy may be appropriate, such as pancreatic neuroendocrine tumours), and is also required for most clinical trials and when the diagnosis of malignancy is unclear.

Tumour markers

The serum tumour marker carbohydrate antigen (CA) 19-9, which binds to the tumour surface marker sialyl-Lewis^A, is often used in pancreatic cancer management for assessing treatment benefit.[13] It has limited specificity and sensitivity, and is not produced by patients lacking the blood Lewis antigen, so it has only a minor role in diagnosis. However, CA 19-9 levels greater than 130 U/mL may predict unresectable disease, and very high levels may indicate the presence of occult metastatic disease, even when disease is localised on imaging. In this situation, further investigations, such as PET/CT and staging laparoscopy, should be employed.

Surgical definitions

Standardisation of surgical definitions allows clearer comparison of surgical and oncological outcomes. International guidelines published in 2014 categorise the nomenclature for surgical procedures, vascular resection and lymph node resection.[14,15] The pre-operative classification of resectability has significant impact on which patients undergo surgery, whether surgery should be performed at a unit experienced in vascular resection, and whether neo-adjuvant treatment should be employed. Similarly, standardisation of specimen handling and the definition of a clear surgical margin aids comparison of different treatments and outcomes, which is paramount when conducting clinical trials or assessing and benchmarking outcomes.

Pre-operative classification of resectability

The decision to perform surgery is based on all available pre-operative information and the assessment of whether clear margins can be achieved. Current guidelines do not discriminate between tumours that do or do not require portal vein resection to achieve a clear margin, despite differences in outcomes and morbidity.[16,17] There is also no differentiation regarding the borderline resectability of the venous and arterial margins. The panel recommends classification of operability into five categories, as the most commonly used international guidelines differ and do not account for the need for vascular resection, the likelihood of obtaining a clear margin, or differences in survival for these patient groups:

1a) clearly resectable tumours with a standard pancreatectomy;

1b) clearly resectable tumours that may require portal venous resection;

2a) borderline resectable tumours that require venous resection;

2b) borderline resectable tumours that require arterial resection; and

3) locally advanced inoperable tumours or metastatic disease.

Detailed information about the criteria for each category is available in the full report of the Workshop.[7]

The multidisciplinary team

The increasing complexity of cancer care and the implementation of multimodality treatment of pancreatic adenocarcinoma highlight the value of a specialist multidisciplinary team (MDT) meeting. This should result in increased numbers of patients receiving optimal personalised management and appropriate surgical treatment, and more frequent recruitment to clinical trials. The MDT discussion should include an experienced lead clinician as

well as broad surgical, medical and radiation oncology, palliative care, genetics, nursing and allied health expertise, especially in the area of nutrition. Each patient should be presented to the MDT by a senior clinician responsible for the patient, who represents the interests of the patient and ensures that decisions made by the MDT are implemented. Workshop panel members recommended that all patients with pancreatic cancer should be registered, that their demographic details and the extent of disease be documented, and that this should be formally presented at an MDT meeting; however, this may not always be practical. Patients with widespread metastatic disease should be registered to ensure later tracking of treatments and outcomes; their discussion and management may be triaged to an alternative multidisciplinary forum, such as a medical oncology review meeting.

The group of patients presented to an MDT should include:

- all newly diagnosed patients who have potentially operable disease (including borderline resectable) and initially locally advanced (unresectable) disease;
- patients for whom there is diagnostic uncertainty, or uncertainty about how to proceed with their management; and
- patients with single organ metastatic disease or recurrence.

Network arrangements, such as virtual meetings, can ensure that patients from private hospitals and regional centres are not disadvantaged in terms of access and expertise. These networks add value to discussions about these patients, especially for borderline cases and clinical trials.

Surgical procedures

Pancreatic resection should be performed after adequate pre-operative staging and assessment of fitness for surgery. All pancreatic resections carry the risk of significant morbidity and mortality, and should only be undertaken in experienced pancreatic surgical units.[18] The standard procedure for a pancreatic head or uncinate process tumour is a Whipple procedure (pancreaticoduodenectomy), including removal of associated lymph nodes.[14,15] For tumours of the body or tail of the pancreas, a subtotal or distal pancreatectomy (with splenectomy) is the standard procedure. Extended pancreatectomy (when associated vascular resection is performed) can be completed with survival rates similar to those of standard resections, but should be limited to specialist units with experience in vascular reconstruction.[19,20] The general consensus among panel members was that extended multivisceral and arterial resections should be performed only in exceptional circumstances, because of the associated increase in morbidity and mortality.[16,17]

Specimen handling and pathological reporting

At present, the definition of a clear tumour resection margin is not internationally standardised. Many centres in Australia and Europe define an R0 resection (no tumour cells within a defined distance from the margin) as one without evidence of tumour within 1 mm of the edges of the resection margin, but some centres still use a 0 mm definition (ie, no evidence of tumour cells at the margin). While meeting the first definition is associated with significantly improved survival, a clear margin by either definition is correlated with better outcomes than involved margins.[21,22] A recent systematic review found that varying definitions of clear margins had a significant impact on R0 resection rates in pancreatic cancer surgery (49% for a 1 mm margin, compared with 72% for a 0 mm margin).[23] This review also reported that inconsistent use of terminology, lack of agreement on structured reporting guidelines, and variations in pathological techniques (axial slicing *v* other slicing techniques) hampered comparative analysis of the outcomes of international studies and identifying optimal pathways of care.

The Workshop recommended adoption of the Royal College of Pathologists of Australasia guidelines, as they reflect best practice and are easily reproducible. A resection specimen is considered R0 if all seven surgical margins are clear from 1 mm. However, regardless of the R status, the microscopic clearance of critical margins (ie, superior mesenteric artery, pancreatic transection, and superior mesenteric vein/portal vein margins) must be recorded in the pathology report. The use of a structured pathology reporting protocol that standardises the reporting of surgical margin status and other relevant information, such as depth of portal vein invasion, is recommended.[21]

Neo-adjuvant therapy

In Australia (and internationally) some centres use pre-operative neo-adjuvant therapy in patients with borderline resectable disease,[24] and there is evidence for improved survival outcomes for patients with resectable and borderline resectable pancreatic cancer.[25] Interpretation of these data is complicated by inconsistent or imprecise definitions of resectability, the rapid evolution of chemotherapy agents, and their combined use with radiotherapy. These confounding factors have resulted in confusion when interpreting patient outcomes associated with neo-adjuvant therapy.

Neo-adjuvant therapy and clearly resectable disease

Active research is currently being conducted in this area. The Australian gemcitabine and nab-paclitaxel (GAP) study[26] examined the feasibility of giving pre- and post-operative chemotherapy to patients with resectable pancreatic cancer. The results indicated that pre-operative treatment (gemcitabine—nab-paclitaxel) was safe, did not impair the ability to perform surgery, and improved the R0 resection rate for patients with resectable disease. The study also found that post-operative chemotherapy was given to only 60% of patients, whereas pre-operative treatment was administered to 93% of patients,

reflecting experience elsewhere.[26] Although it can be considered for patients with clearly resectable pancreatic adenocarcinoma, the ultimate survival benefit of this approach remains to be established, and patients should be referred for clinical trials whenever possible.

Neo-adjuvant therapy and borderline resectable disease

Although several overviews have suggested the benefits of neo-adjuvant chemotherapy,[25,27] variability in definitions has caused substantial uncertainty about whether it has a significant impact on resectability or curability in the borderline setting. The choice of chemotherapy or chemoradiation remains unclear. It has been reported that FOLFIRINOX (folinic acid–fluorouracil–irinotecan–oxaliplatin) and gemcitabine–nab-paclitaxel achieve objective shrinkage of primary tumours in small numbers of patients. Similarly, the addition of radiotherapy may lead to downstaging to operability for some patients. In this setting, however, re-imaging of local disease is unreliable, and patients should be re-evaluated by the MDT with respect to surgery, even in the absence of metastatic disease.[28] Given the lack of clarity about the benefits, patients with borderline tumours should be offered the opportunity to participate in clinical trials.

Neo-adjuvant therapy and locally advanced disease

Chemotherapy is recommended as the initial therapy for the management of patients with unresectable locoregional pancreatic cancer. The value of adding radiation after initial chemotherapy remains uncertain. However, downstaging chemoradiation is an option, although its use in this population is controversial; some patients are medically unfit for such intensive treatment, and it should usually be offered in the context of a clinical trial.[27]

Conclusion

The treatment of operable pancreatic cancer is entering a new phase of multimodal therapy in an attempt to improve upon the limited benefit of surgery alone. The considerable difficulties encountered in comparing studies and evaluating the quality of care will continue unless we have clear and precise definitions of a complete resection margin (preferably 1 mm R0), and of the choice of surgical procedures and pre-operative resectability criteria, as well as structured pathology and radiology reporting and compulsory MDT registration. Implementing a structured approach, as outlined in this article, is an essential step toward improving the care and outcomes for patients with pancreatic cancer in Australasia.

Acknowledgements: The AGITG received funding from the Avner Nahmani foundation, a charitable organisation devoted to improving survival of people with pancreatic cancer by funding research.

Competing interests: David Goldstein is an unremunerated advisor to Bayer, Celgene, Amgen, Roche and Pfizer, and has received research funding for his institution from Celgene, Pfizer and Amgen. He is the treasurer and a board member of the AGITG. Andrew Barbour is an unremunerated advisor to Celgene and unpaid member of the AGITG Scientific Advisory Committee. The AGITG funded all travel.

Provenance: Not commissioned; externally peer reviewed. ■

References are available online at www.mja.com.au.

1 Australian Institute of Health and Welfare. Pancreatic cancer in Australia. http://www.aihw.gov.au/cancer/pancreatic/ (accessed Apr 2016).

2 Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; 350: 1200-1210.

3 Burmeister EA, O'Connell DL, Beasley VL, et al. Describing patterns in pancreatic cancer: a population-based study. *Pancreas* 2015; 44: 1259-1265.

4 Howard TK, Krug JE, Yu J, 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 Gastrintest Surg* 2006; 10: 1338-1345.

5 Allison DC, Piantadosi S, Hruban RH, et al. DNA content and other factors associated with ten-year survival after resection of pancreatic cancer. *J Surg Oncol* 1998; 67: 151-159.

6 Sohn TY, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas — 616 patients: results, outcomes and prognostic indicators. *J Gastrointest Surg* 2000; 4: 567-579.

7 Australasian Gastro-Intestinal Trials Group. Definition of surgical standards for pancreatic cancer: a consensus statement. 2016. http://agitg.org.au/files/2016/02/AGITG-Pancreatic-Cancer-Surgical-Guidelines-Report-2015.pdf (accessed Apr 2016).

8 Shrikhande SV, Barreto SG, Goel M, Arya S. Multimodality imaging of pancreatic ductal adenocarcinoma: a review of the literature. *HPB (Oxford)* 2012; 14: 658-668.

9 Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. *Gastroenterology* 2012; 146: 291-304.e1.

10 Burge ME, O'Rourke N, Cavallucci D, et al. A prospective study of the impact of fluorodeoxyglucose positron emission tomography with concurrent non-contrast CT scanning on the management of operable pancreatic and peri-ampullary cancers. *HPB (Oxford)* 2015; 17: 624-631.

11 Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA. How good is endoscopic ultrasound-guided fine needle aspiration in diagnosing the correct etiology for a solid pancreatic mass? A meta-analysis and systematic review. *Pancreas* 2013; 42: 20-26.

12 Iglesias-Garcia J, Dominguez-Munoz JE, Abdulkader I, et al. Influence of on-site cytopathology evaluation on the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of solid pancreatic masses. *Am J Gastroenterol* 2011; 106: 1705-1710.

13 Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006; 24: 5313-5327.

14 Tol JAMG, Gouma DJ, Bassi C, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). *Surgery* 2014; 156: 591-600.

15 Hartwig W, Vollmer CM, Fingerhut A, et al. Extended pancreatectomy in pancreatic ductal adenocarcinoma: definition and consensus of the International Study Group for Pancreatic Surgery (ISGPS). *Surgery* 2014; 156: 1-14.

16 De Reuver PR, Mittal A, Neale M, et al. Extended pancreatoduodenectomy as defined by the International Study Group for Pancreatic Surgery is associated with worse survival but not with increased morbidity. *Surgery* 2015; 158: 183-190.

17 Tempero MA, Malafa MP, Behrman SW, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw* 2014; 12: 1083-1093.

18 De Wilde RB, Van der Tweel I, De Hingh IH, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. *Br J Surg* 2012; 99: 404-410.

19 Murakami Y, Satoi S, Motoi F, et al. Portal or superior mesenteric vein resection in pancreatoduodenectomy for pancreatic head carcinoma. *Br J Surg* 2015; 102: 837-846.

20 Ravikumar R, Sabin C, Abu Hilal M, et al. Portal vein resection in borderline resectable pancreatic cancer: a United Kingdom multicenter study. *J Am Coll Surg* 2014; 218: 401-411.

21 Royal College of Pathologists of Australasia. Cancer of the exocrine pancreas, ampulla of Vater and distal common bile duct. Structured reporting protocol. Sydney: RCPA, 2014. https://www.rcpa.edu.au/getattachment/3b6a41df-939d-492e-bc6b-35fc264bd89b/Protocol-pancreatic-cancer.aspx (accessed Apr 2016).

22 Hartwig W, Hackert T, Hinz U, et al. Pancreatic cancer surgery in the new millennium: better prediction of outcome. *Ann Surg* 2011; 254: 311-319.

23 Chandrasegaram MD, Goldstein D, Simes J, et al. Systematic review and meta-analysis of R0 rates and margin assessment in pancreatic cancer. *Br J Surg* 2015; 102: 1459-1472.

24 Heineman VH, Haas M, Boeck S. Neoadjuvant treatment of borderline resectable and non-resectable pancreatic cancer. *Ann Oncol* 2013; 24: 2484-2492.

25 Andriulli AF, Festa V, Botteri E, et al. Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. *Ann Surg Oncol* 2012; 19: 1644-1662.

26 Barbour A, O'Rourke N, Samra S, et al. A multicenter, phase II trial of preoperative gemcitabine and nab-paclitaxel for resectable pancreas cancer: The AGITG GAP study [abstract]. *J Clin Oncol* 2015; 33 Suppl: abstract 4115. http://meetinglibrary.asco.org/content/143994-156 (accessed Apr 2016).

27 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: 618-625.

28 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: 28-33. ■