AUSTRALASIAN GASTRO-INTESTINAL TRIALS GROUP

Definition of surgical standards for pancreatic cancer: A consensus statement by the Australasian Gastro-Intestinal Trials Group

Background

The lack of accepted and widely used definitions of operability of patients with pancreatic adenocarcinoma hampers the thorough analysis of this patient group. Varying definitions of resectability and unresectability can influence patient outcomes – clearer definitions of resectability will help prevent unnecessary operations from being performed. This can also make it difficult to compare studies, in particular studies that include neo-adjuvant therapy.

To facilitate the development of consensus statements for defining when a patient is clearly operable, borderline or locally advanced/inoperable in an Australian setting, the Australasian Gastrointestinal Trials Group (AGITG) Pancreatic Cancer Surgical Guidelines Workshop was convened in July 2015 by the Australasian Gastro-Intestinal Trials Group (AGITG) in partnership with the Avner Pancreatic Cancer Foundation.

The objectives of the workshop were to:

- provide an overview of local and international guidelines which define operability and R0 resection(microscopic clear margins)
- Develop a consensus statement that defines when a patient is clearly operable, borderline and locally advanced inoperable
- develop an understanding of the circumstances around the use of neo-adjuvant therapies and chemotherapy and in some centres pre-operative radiation
- provide an understanding of the use of multidisciplinary tumour groups to set treatment plans.

A standard definition for resectability will assist hospitals, pancreatic cancer treatment groups and individual surgeons in the decision-making processes. Furthermore, standardisation will enable comparative analysis of studies involving surgery for pancreatic adenocarcinoma.

Pre-operative neo-adjuvant treatments and multidisciplinary tumour groups in the management of pancreatic adenocarcinoma were also discussed to broaden understanding of the circumstances around their use.

The panel was made up of medical experts from around Australia, including surgeons, medical oncologists, radiologists, pathologists and gastroenterologists.

Setting the scene

Pancreatic adenocarcinoma is the ninth most common cancer in men and the tenth most common in women in Australia (Australian Cancer Council 2015). The disease has a poor prognosis with overall survival at 5 years around 6% (Australian Institute of health and Welfare 2014).

The early systemic spread of pancreatic adenocarcinoma and the local invasion of adjacent vessels and organs often limit resectability. Surgery is rarely a cure for pancreatic adenocarcinoma; however, it can improve overall survival of eligible patients.

Although 5-year survival in those who have local or regional involvement remains a low 15%–20%, it is significantly better than the 5-year survival of 3% in people with metastatic disease. Internationally about 20% of patients have potentially resectable disease after staging (Butturini et al 2008), recent Australian data shows that about 15% of patients have surgery (Burmeister et al 2015).

Negative or tumour-free surgical margins, as well as tumour size, lymph node status and absence of metastases are important prognostic indicators for long-term patient survival (Allison et al 1998; Sohn et al 2000; Howard et al 2006).

The National Comprehensive Cancer Network (NCCN) guidelines (2015) delineate resectable, borderline and locally advanced tumours based upon arterial and/or venous involvement and include details depending on whether the tumour is located in the head or tail of the pancreas (Table 1).

The R classification system is used to define the margin of resection in pancreatic adenocarcinoma. At present, the definition of a clear margin is not standardized world-wide. Many centres in Australia and Europe define an R0 resection as no microscopic evidence of tumour within 1 millimetre of the edges of the resected specimen, whereas some centres still use the 0 millimetre minimum margin definition (Hartwig et al 2011; RCPA 2014).

A recent systematic review showed that varying definitions of clear margins significantly impacted the rate of R0 resection rates in pancreatic cancer surgery (49% for a 1 millimetre margin versus 72% for a 0 millimetre margin). (Chandrasegaram et al 2015). This review also reported that inconsistent use of terminology, lack of agreement on structured reporting guidelines and variation in pathological techniques (axial slicing versus other slicing techniques) hampered comparative analysis of the outcomes of international studies.

Chandrasegaram et al concluded ‘there is urgent need for international consensus definitions on margin assessment and synoptic pathological reporting to permit comparative analysis of future international clinical trials.’

The International Study Group of Pancreatic Surgery (ISGPS) recently developed a consensus statement suggesting a 1 millimetre margin for R0 resection with recommendations on minimum reporting on seven margins (anterior, posterior, superior mesenteric vein groove, superior mesenteric artery, bile duct and enteric margins; Bockhorn et al 2014). While reporting of these margins will facilitate comparative studies in pancreatic cancer, the various margins do not carry equal prognostic significance. For example, Jamieson et al (2010) reported no prognostic significance associated with involvement of the anterior and posterior margins.

Although the 1 millimetre margin clearance for an R0 resection being is increasingly endorsed, a more rigorous margin clearance of 2 millimetres has recently been proposed as a superior prognostic factor for overall survival (Gebauer et al 2015).

About these consensus guidelines

These guidelines provide consensus statements that define the resectability of pancreatic adenocarcinoma; that is, the probability of obtaining an R0 resection (defined as ≥1 mm with axial slicing), relevant to an Australasian setting.

Panel members agreed that the statements developed in this report are recommendations developed with the best available evidence and expert opinion, recognising in some areas that no clear evidence exists. These recommendations are provided as a guideline for those working in this field.

Definitions for operable/resectable, borderline resectable and locally advanced inoperable pancreatic cancer were developed.

Imaging for diagnosis/staging, pathology reporting, neo-adjuvant treatment, multidisciplinary tumour groups and treatment plans were also discussed.

Objective

The objective of this report, using the available evidence, is to develop Australian consensus definitions on margin assessment for pancreatic adenocarcinoma by defining operability and R0 and R1 sections.

Consensus definitions for operability will assist multidisciplinary teams in the decision-making process around treatment and care of patients. In principle, this will also progress treatment options for patients as well as facilitate comparative analyses and interpretation of future clinical trials.

Radiology

Imaging for diagnosis/identification of operability

Imaging of the pancreas is the primary means by which the stage of pancreatic adenocarcinoma is determined. It is performed at presentation and following neo-adjuvant treatment to provide adequate staging and assessment of the resectability status of a patient.

Staging for pancreatic adenocarcinoma is based on the TNM classification system described by current editions of the American Joint Committee on Cancer (AJCC) and the International Union of Cancer Control guidelines (AJCC 2010).

Imaging methods that can be used for diagnosis of pancreatic adenocarcinoma include the pancreatic protocol computed tomography (PPCT), endoscopic ultrasound (EUS), magnetic resonance imaging (MRI) and positron emission tomography (PET).

PPCT is the modality of choice for diagnosis and staging, and it outperforms EUS and MRI in terms of accurate staging. PPCT has high sensitivity and best highlights pancreatic lesions and vascular anatomy, in particular involvement of major vessels around the tumour which play a major role in determining resectability.

The Group recommends following the NCCN radiology guidelines for a PPCT. These include a precontrast scan, an arterial phase, a pancreatic parenchymal (late arterial phase to delineate tumour and show arteries) and a portal venous phase. Acceptable alternatives according to local practice include:

- a precontrast scan, an arterial phase and a portal venous phase, or
- a precontrast scan, a pancreatic parenchymal (late arterial phase to delineate tumour and show arteries) and a portal venous phase.

The sensitivity and accuracy of CT for staging pancreatic adenocarcinoma is high and does not appear to vary between the different types of CT scanners used (Zamboni et al 2007). However, imaging at high-volume centres may be more accurate. A recent study demonstrated management of most patients who underwent further imaging within a high-volume centre was altered (mostly upstaging of resectable to borderline or borderline to unresectable; Walters et al 2011).

EUS has variable sensitivity and accuracy for staging of pancreatic adenocarcinoma (<60% sensitivity). It is operator-dependent and therefore unable to be standardised across institutes. However, the EUS is the most sensitive test for detecting small lesions which are undetectable on CT or MRI (Wang et al 2013a) and is best used as an adjunct or complementary modality to PPCT. EUS plays a larger role in diagnosis and tissue acquisition rather than staging.

In comparison to CT, greater soft-tissue contrast can be appreciated on MRI. Metastasis are usually hypovascular with low fluid content. Therefore, MRI has greater sensitivity for detecting and characterising liver metastasis. and when suspected pancreatic tumours are not visible on CT.

The role of PET in staging for pancreatic adenocarcinoma is unclear (Wang et al 2013b).). A recent Australian study observed that PET may change management for fluorodeoxyglucose (FDG)-avid lesions; however, only about 75% of pancreatic tumours are FDG-avid. When combined with CT, PET showed increased sensitivity and changed management in 11% (Farma et al 2008) and 16% (Burge et al 2015) of patients.

Recommendations

Pancreatic protocol computed tomography within four weeks of diagnosis should be performed for tumour-node-metastases staging and assessing resectability before presentation to the multi-disciplinary team.

If no metastatic disease is detected the decision about whether a tumour is resectable, borderline or nonresectable should be made by consensus at a multi-disciplinary team meeting.

If imaging shows metastases, no further scanning is required and a biopsy should be conducted to confirm diagnosis (in this circumstance a non-pancreatic protocol computed tomography may be acceptable).

Staging investigations should be conducted prior to biopsy or stenting, as the presence of haematoma, stent artefact or pancreatitis reduces the ability to accurately define resectability.

When lesions are small (less than 1 cm), the sensitivity of the pancreatic protocol computed tomography is reduced and the endoscopic ultrasound method should be used to complement computed tomography results for enhanced diagnosis. Endoscopic ultrasound plays a role more so in diagnosis and tissue acquisition than in staging.

If tissue resolution with the pancreatic protocol computed tomography is not clear (isodense pancreatic tissue or cystic lesions) or no mass is visible but the patient is jaundiced (potential liver involvement) then magnetic resonance imaging should be performed to improve visual acuity to increase diagnostic capability for malignancy.

Magnetic resonance imaging and positron emission tomography, if available, may be considered prior to resection to reduce risk of occult malignancy.

Endoscopic Ultrasound

Biopsy

Confirmation of malignancy with biopsy is considered necessary for patients with metastatic disease and locally advanced tumours prior to commencing chemotherapy. It is also considered necessary in patients with borderline resectable disease being considered for neoadjuvant chemotherapy. When a diagnosis of autoimmune pancreatitis is suspected, a biopsy is recommended and a short course of steroid treatment should be considered if the biopsy does not reveal features suspicious for malignancy.

In the presence of a solid, resectable mass suspicious for malignancy, consensus was reached that biopsy proof is not required before proceeding with resection. However, panel members felt that tissue diagnosis is advisable in these patients when it can be safely performed before major surgical intervention as it may alter treatment decisions in a small number of patients. Thus, biopsy is desirable but not mandatory in resectable cases.

Tissue can be taken by passing a fine-needle under EUS guidance (EUS-FNA) or under CT guidance. However, EUS-FNA has a lower risk of tumour seeding and thus is the preferred method of obtaining tissue. (Puli et al 2013).

Successful predictors of diagnostic yield of EUS-guided biopsy in pancreatic cancer include:

- experience of endoscopist
- number of passes of needle through tumour
- needle size
- presence of onsite cytologist/cytolopathologist.

Enhanced imaging techniques such as intravenous contrast can be used during EUS, although these are not yet widely available.

The risks associated with EUS-guided biopsy include pancreatitis (less than 2%) and needle-track seeding. In patients with definitive solid pancreatic body and tail tumours the risks of biopsy may outweigh its benefits in technically resectable cancers.

Although biopsy carries a small chance of pancreatitis and sampling error, a tissue diagnosis does address psychological components of this disease for patients and the treating physician. Conversely, a negative biopsy result, either non-diagnostic/inadequate or inconclusive, can make it difficult to convince a patient of the need for pancreatectomy when imaging shows an obvious tumour. Hence, while histological diagnosis is desirable for all patients with pancreatic cancer, multiple attempts to repeat biopsy in resectable may not be advisable and should be made on an individual basis.

In the past, the position of a tumour determined the size of the needle used for biopsy. Tumours in the tail or body of the pancreas could be biopsied using a larger needle because of the straighter endoscope position. Smaller needles are better for manoeuvring through the endoscope, particularly if the endoscope is in a looped position (Chen et al 2012). For example, lesions in the uncinate process and the distal liver require the endoscope to be looped which may pose difficulty in passing large gauge needles. Therefore, smaller needles (22g or 25g) are generally used for uncinate lesions.

The recent availability of more flexible larger needles (19G and 20G) that can be manoeuvred through a looped-scope position enable tissue to be obtained from lesions in more difficult to get to positions (e.g. uncinate) (Young Bang et al 2012). This is particularly relevant if core specimens are required.

Larger needles (19G) may facilitate core specimen acquisition; however, this also results in blood contaminated specimens. Smaller needles (22 or 25G) enable high diagnostic yield with lower amounts of blood contamination. However, increased number of passes may be required to obtain enough tissue for cell block and immunohistochemistry.

The presence of a cytologist during the biopsy procedure improves diagnostic yield (Iglesias-Garcia et al 2011). The cytologist can assess tissue on a slide immediately and determine whether further samples are needed.

Limitations

There is a challenge in obtaining enough biopsy tissue for pathology laboratories to render an accurate cytological or histological diagnosis as well as having residual material available for molecular analyses.

Cytology-based techniques are time consuming, technically demanding and only assess tumour cell morphology. Stromal components of pancreatic cancer are now known to be important in determining whether tumours will respond to certain therapies.

Molecular profiling of tumours is an evolving area for typing pancreatic cancer (Brais et al 2012). The K-ras mutation is present in up to 90% of pancreatic cancers and can be used to differentiate between a benign and malignant mass (Waddell et al 2015).

Recommendations

Endoscopic ultrasound-guided fine needle aspiration or core biopsy is the method of choice for obtaining tissue from lesions suspected to be pancreatic adenocarcinoma.

Endoscopic ultrasound fine needle aspiration/core biopsy should be performed and a diagnosis of pancreatic adenocarcinoma confirmed where neo-adjuvant chemotherapy/radiotherapy is considered.

Endoscopic ultrasound fine needle aspiration/core diagnosis of pancreatic adenocarcinoma may be desirable prior to pancreatectomy or palliative treatment. In the setting of metastatic disease, prior to palliative chemotherapy, biopsy could also be obtained and perhaps preferred when accessible with percutaneous guided access of liver lesions.

Perform endoscopic ultrasound rather than percutaneous biopsy of the pancreas before surgery to obtain better diagnostic yield, safety, and reduce risk of peritoneal seeding.

If possible, have a cytologist or cytotechnician present during the biopsy procedure.

Surgery

Achieving a negative margin or R0 resection in pancreatic adenocarcinoma requires meticulous surgery and is dependent on the stage and to a lesser extent on the site of the tumour.

Resectable tumours have little or no abutment with the vasculature – arteries (superior mesenteric artery (SMA), coeliac artery (CA) or hepatic artery (HA)) and veins (superior mesenteric vein (SMV), portal PV).

Abutment of the tumour on vessels or involvement of the vasculature reduces the probability of getting an R0 resection. Current guidelines usually consider encasement/involvement of the SMA/celiac trunk to indicate unresectable disease (NCCN Guidelines, 2015).

Metastatic disease and involvement of other organs usually indicates unresectable disease.

Definitions of surgical procedures

Pancreaticoduodenectomy (Whipple procedure)

Pancreaticoduodenectomy (PD) is the most commonly performed procedure for patients with right-sided lesions of the pancreatic head or uncinated process (Figures 1 and 2). A standard PD includes en bloc resection of the head of the pancreas, duodenum, proximal jejunum, distal stomach, gall bladder and common bile duct and regional lymph nodes.

Reconstruction of gastrointestinal continuity requires pancreaticojejunostomy or pancreaticogastrostomy, choledochojejunostomy, and gastrojejunostomy. To date, no reconstructive option for pancreaticojejunostomy shows clear superiority over another and hence remains the choice of the surgeon based on their experience (Wolf and Lavu, 2012).

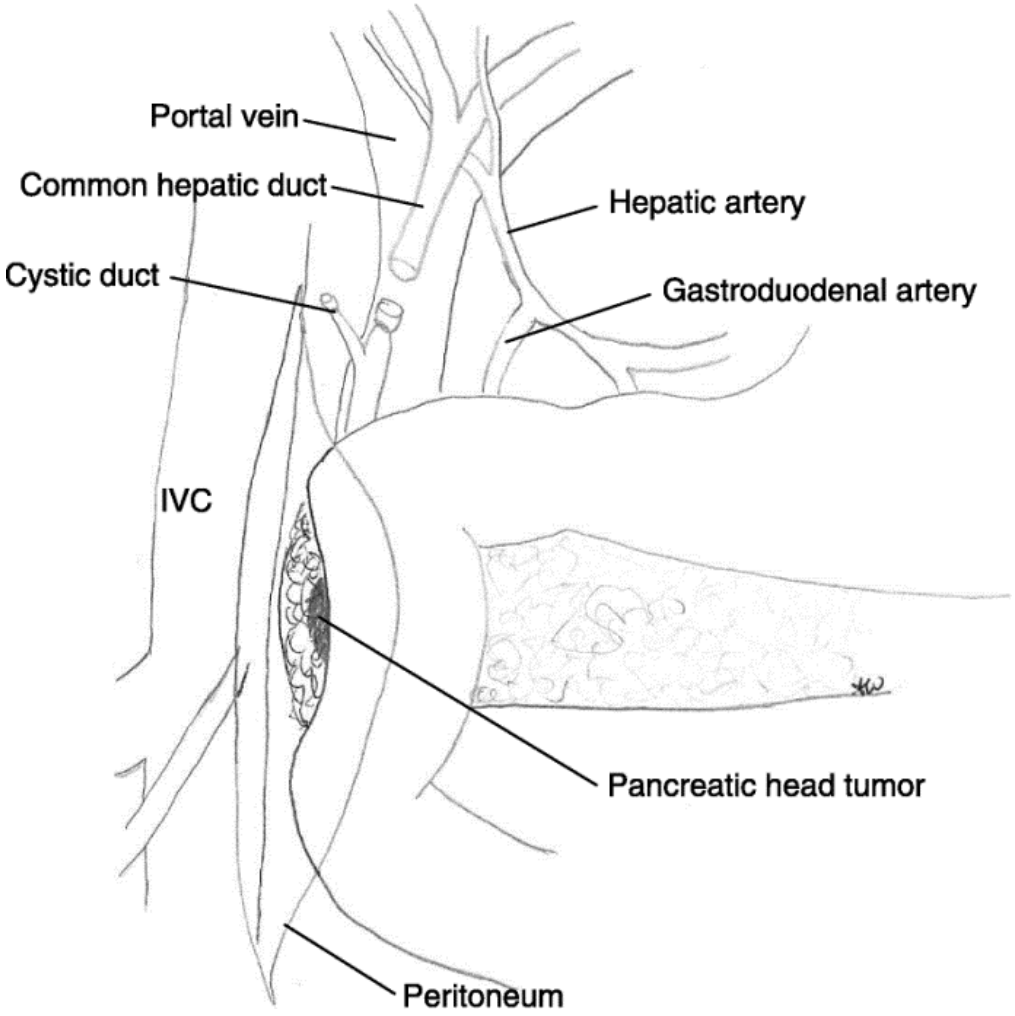

Figure 1: Anatomy of blood vessels and organs located near a tumour confined to the head of the pancreas. The Whipple surgical procedure is commonly used to treat pancreatic tumours located in the head of the pancreas. IVC = inferior vena cava.

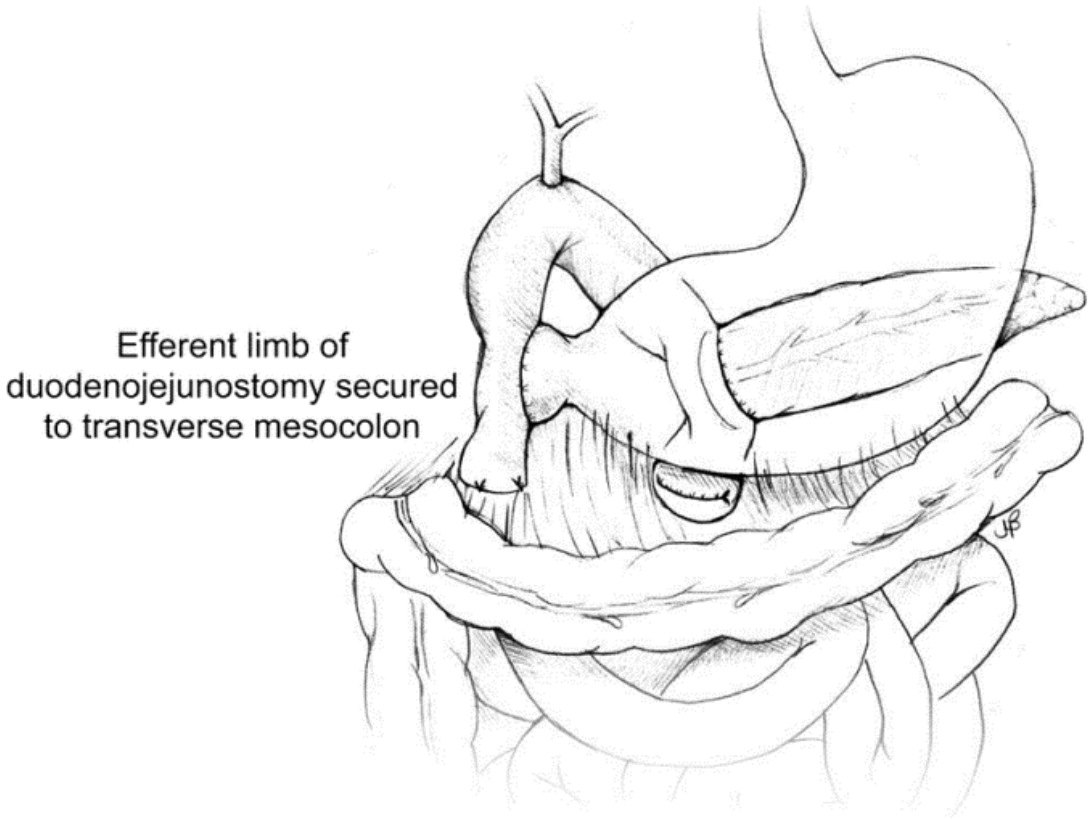

Figure 2: Diagram showing the reconstruction following a pylorus preserving pancreatoduodenectomy for pancreatic cancer. The head of the pancreas, the duodenum, a portion of the common bile duct, gallbladder, and sometimes part of the stomach are removed. After surgery the remaining portions of the digestive system are reattached for functional digestion. Images reproduced with permission from the article 'Pancreaticoduodenectomy and its variants' by Wolf AM and Lavu H published in *The Cancer Journal* 2012, 18(6):555-561.

A modification of the standard PD involves preservation of the pylorus, known as pylorus-preserving pancreaticoduodenectomy (PPPD). This aim of this procedure being to reduce nutritional side effects such as weight loss, dumping syndrome, or diarrhoea. However, it is unclear whether PPPD provides a nutritional benefit compared with PD.

The standard PD resection may include regional or standard lymphadenectomy around the duodenum and pancreas. A lymphadenectomy beyond the abovementioned area could therefore be considered an extended lymphadenectomy.

Distal (left side) pancreatectomy

Less than 10% of patients with left-side pancreatic adenocarcinoma are considered eligible for surgery. For those patients with tumours that are confined to the pancreas, distal pancreatectomy with en bloc resection of the spleen is the standard operation. Splenic preservation is not appropriate for patients with suspected pancreatic adenocarcinoma.

Standard left-sided resections include the distal pancreatectomy and radical antegrade modular pancreatosplenectomy (RAMP).

RAMP can be more difficult to achieve because of the late stage at which these cancers are discovered. This resection can involve the body and/or tail of the pancreas, the spleen, including splenic vessels, lymphadenectomy, sometimes fascia of Gerota, and sometimes elements of the transverse mesocolon.

Total pancreatectomy may be required in a small subset of patients, particularly those with pancreatic neck tumours, but should be restricted to specialised units.

Lymphadenectomy

The lymph node status of patients with resectable pancreatic ductal adenocarcinoma is an important predictor of survival.

Standard lymphadenectomy during PD or pancreatectomy is recommended as defined in a consensus statement developed by the International Study group on Pancreatic Surgery: 'Standard lymphadenectomy for pancreatoduodenectomy should strive to resect lymph node stations no. 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b. For cancers of the body and tail of the pancreas, removal of stations 10, 11, and 18 is standard' (Tol et al 2014).

The standard PD may comprise of regional lymphadenectomy around the duodenum and pancreas, including the lymph nodes on the right side of the hepatoduodenal ligament, the right side of the superior mesenteric artery, and the anterior and posterior pancreaticoduodenal lymph nodes. However, no significant survival advantage is obtained from extended lymphadenectomy (Iqbal N et al 2009).

Extended resection

Extended resection remains an area of controversy. This is clearly defined in the ISGPS guidelines; however, the benefits and risks may need more investigation. For example:

- venous resection
- arterial resection
- multivisceral resection.

Pancreatoduodenectomy, along with portal vein resection, is increasingly performed to resect pancreatic cancer and, as the ISGPS guidelines state, this constitutes an extended resection (Hartwig W et al 2014). Patients undergoing PV and SMV resections generally have similar survival outcomes to patients who have standard resections (Ravikumar et al 2014, Murakami et al 2015). Further analysis has shown that some of these patients may have a poorer survival outcome not because of the PV resection, but due to adverse biology associated with these tumours given their topography (Wang et al 2014).

There was consensus amongst panel members that extended resection operations, particularly those requiring major vascular reconstruction, should be performed by experienced pancreatic surgeons in centres where appropriate expertise is available for vascular reconstruction. If, based on imaging studies, extended resections appear necessary to achieve complete tumour excision, patients should be referred to a center with appropriate expertise without the need to confirm findings by prior surgical exploration.

The general consensus amongst panel members was not to resect the SMA as arterial resection is associated with increased morbidity and mortality. There is a paucity of data to support arterial resection increases survival over palliative chemotherapy.

Multi-visceral resection beyond the organs considered part of a standard pancreatectomy (e.g. pancreas, duodenum, jejunum, gallbladder, bile duct +/- stomach for right side resections; and pancreas and spleen for left side resections) is also considered to be associated with increased morbidity and mortality. However, portal vein/superior mesenteric vein and some visceral involvement (stomach, small bowel beyond the first segment of jejunum, colon and/or mesocolon, right adrenal, right kidney, liver, diaphragmatic crura) was considered borderline resectable. In exceptional circumstances, after multidisciplinary discussion, a surgeon may wish to perform an extended pancreatectomy which may include resection arterial structures, non-contiguous abdominal organs or limited non contiguous metastatic disease.

Consensus statements

Operable/resectable pancreatic cancer

Panel members proposed two categories for patients with resectable pancreatic adenocarcinoma for the purposes of clinical studies, including clinical trials. We recommend adherence to the NCCN guidelines with the recognition of several issues outlined below (see Table 1).

Whilst all patients in this category are considered resectable, they can be divided into two subgroups:

- Group 1 includes patients who do not require venous vascular resection/reconstruction to obtain R0 resection with a high likelihood
- Group 2 includes patients who may require PV vascular resection/reconstruction, and as a consequence there is a higher morbidity in this patient group.

Patients with resectable tumours showing no involvement of the PV (Group 1) are considered a different biological group and separating these patients facilitates appropriate treatment choices, clinical studies and comparability of patients between MDTs/hospitals.

Borderline resectable pancreatic cancer

Patients were considered to have borderline resectable pancreatic cancer (low probability to achieve R0, but R1 resection possible) based on PPCT criteria.

Panel members agreed to divide individuals with borderline resectable disease into two patient groups because involvement of the veins or arteries were considered different biological groups, which facilitates appropriate treatment choices, clinical studies and in a trial situation this would allow for clarity and reproducibility of results between MDTs/hospitals.

Borderline resectable group 1 includes patients who require venous vascular resection/reconstruction and/or resection of adjacent organs not considered part of a standard pancreatic resection; and borderline resectable group 2 includes patients who require arterial vascular resection/reconstruction (see Table 1).

Neo-adjuvant treatment should be considered for patients with borderline resectable disease. This remains an investigational approach with no randomised data to support its utility in altering survival. In addition, no consensus on whether neoadjuvant therapy should be restricted to chemotherapy or chemoradiation exists. In that light, referral to relevant clinical trials is strongly recommended.

Unresectable/locally advanced pancreatic cancer

Disease is considered inoperable (never able to achieve R0) due to metastatic disease (including non-regional lymph node metastasis), tumour involvement with veins and arteries (see Table 1).

Other factors

Other factors to take into consideration for patients being considered for surgery include:

- medically unfit for surgery
- carbohydrate antigen 19-9 (CA 19-9) levels: high CA 19-9 consideration should be given to give laparoscopy and FDG–PET scan (a very high Ca19-9 level may indicate occult metastatic disease in the setting of a resectable tumour and more thorough assessment, such as repeat CT/MRI/PET staging laparoscopy, may be necessary to diagnose this)
- in pancreatic neck or body tumours involvement of the splenic artery is likely to represent advanced disease – additional staging will help determine curability and consideration given to neo-adjuvant treatment.

Recommendations

Follow NCCN guidelines for unresectable pancreatic cancer.

Consider resectable patients in two groups:

- patients needing portal vein resection
- patients not needing portal vein resection.

Consider borderline resectable patients in two groups:

- patients who require venous vascular resection/reconstruction and/or resection of adjacent organs not considered part of a standard pancreatic resection
- patients who require arterial resection/reconstruction.

Conduct standard lymphadenectomy.

Consider giving neo-adjuvant treatment to patients with borderline resectable disease.

Take level of fitness, carbohydrate antigen 19-9 levels and involvement of splenic artery into account before operating on a patient and/or giving neo-adjuvant treatment.

Table 1: Criteria for defining resectability status in pancreatic adenocarcinoma.

NCCN		**AGITG**	
Resectability status	**Criteria**	**Resectability status**	**Criteria**
Tumours considered localised and clearly resectable	• no distant metastases • no radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion • clear fat planes around the celiac axis, hepatic artery, and SMA.	Tumours considered localised and clearly resectable **Group 1a**: Disease is *clearly* resectable (R0 resection achievable) on the basis of physical examination and CT (or MRI if indicated)	• no distant metastases • no radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion and clear fat planes around these vessels • clear fat planes around the celiac axis, hepatic artery, and SMA • no radiographic evidence of SMA, coeliac artery (CA) or hepatic artery (HA) abutment or distortion
		Tumours considered localised and resectable **Group 1b**: Disease is resectable (R0 resection achievable) *with potential need for PV resection* on the basis of physical examination and CT (or MRI if indicated)	• no distant metastases • no more than 180 degrees of contact with the circumference of the SMV, PV or SMV–PV confluence with loss of fat planes but no evidence of PV infiltration or occlusion/vein contour irregularity • clear fat planes around the celiac axis, hepatic artery, and SMA • no radiographic evidence of SMA, coeliac artery (CA) or hepatic artery (HA) abutment or distortion.
Tumours considered borderline resectable	• no distant metastases • venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement • gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis • tumour abutment of SMA not to exceed greater than 180 degrees of the circumference of the vessel	Tumours considered borderline resectable **Group 2a**	• no distant metastases • venous involvement of the SMV or PV (tumour contact with more than 180 degrees of the circumference of the vessel wall) or distortion/ narrowing/ occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement • involvement of adjacent, but resectable organs such as stomach, transverse colon, kidney • tumour contact with the inferior vena cava • the preferred approach to radiologic resectability should be based upon the soft tissue density tumour

NCCN		AGITG	
Resectability status	**Criteria**	**Resectability status**	**Criteria**
	wall.		abutting vessels but fat stranding should be commented upon.
		Tumours considered borderline resectable **Group 2b**	• no distant metastases • tumour abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall • tumour abutment of the CA not to exceed greater than 180 degrees of the circumference of the vessel wall with no extension to celiac axis or HA bifurcation • gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis. • the preferred approach to radiologic resectability should be based upon the soft tissue density tumour abutting vessels but fat stranding should be commented upon.
Tumours considered locally advanced/ unresectable	**Head** • distant metastases • greater than 180 degrees SMA encasement, any celiac abutment • unreconstructible SMV/portal occlusion • aortic or inferior vena cava (IVC) invasion or encasement. **Body** • distant metastases • SMA or celiac encasement greater than 180 degrees • unreconstructible SMV/portal occlusion • aortic invasion. **Tail** • distant metastases	Tumours considered locally advanced/ unresectable **Group 3**	**Head** • distant metastases • greater than 180 degrees SMA encasement, any celiac abutment • unreconstructible SMV/portal occlusion • aortic or inferior vena cava (IVC) invasion or encasement • **Body** • distant metastases • SMA or celiac encasement greater than 180 degrees • unreconstructible SMV/portal occlusion • aortic invasion. **Tail** • distant metastases

NCCN		AGITG	
Resectability status	**Criteria**	**Resectability status**	**Criteria**
	• SMA or celiac encasement greater than 180 degrees. **Nodal status** Metastases to lymph nodes beyond the field of resection should be considered unresectable.		• SMA or celiac encasement greater than 180 degrees. **Nodal status** Metastases to lymph nodes beyond the field of a standard resection should be considered unresectable.

Pathology

Pathology reporting for pancreatic cancer should involve structured/synoptic reports that include accurate and complete information addressed by pathological data set checklists (mandatory minimum data set and best practice comprehensive data set).

A structured pathology reporting protocol is available for pancreatic cancer that includes standardised elements, terminology and definitions for cancer reporting, etc. (Royal College of Pathologists of Australia (RCPA) 2014 Pancreatic Cancer Reporting Protocol).

Compared with traditional narrative reporting, structured reporting provides more complete information (e.g. margins, pathological stage) and improves the utility of histopathological reports for pancreatic cancer specimens (Gill et al 2009).

The pathology report should include information on the method of specimen handling (e.g. axial slicing versus other slicing methods) and pathological elements (such as dissection, sampling of tumour and normal tissue, inking of margins, microscopic reporting of grade, perineural invasion, lymphovascular invasion, surgical margins, etc.). It is usually recommended that at least 12 lymph nodes be examined (RCPA 2014; AJCC 2010).

In addition, entering basic clinical information onto a standardised pathology request form; for example, type of operation, whether a SMV/portal vein resection has been performed, whether any preoperative chemotherapy has been administered etc, aids accurate pathological assessment of the specimen.

Harmonisation of pathology reporting internationally will facilitate comparison between groups of patients with pancreatic cancer from different centres and enhance clinical understanding of patients. It will also enable the inclusion of cohorts of patients from different centres into the same study or trial, increasing the feasibility of running trials and developing new interventions for this disease.

Standard margins

There are seven standard margins for pancreatic cancer (RCPA 2014; Bockhorn et al 2014). These include:

- pancreatic transection (neck) margin
- SMV/PV margin (vascular groove)
- SMA margin (uncinate)
- posterior margin
- proximal margin (gastric/duodenal)
- distal margin (distal duodenal/jejunal)
- bile duct margin
- +/– portal vein (PV) margin (applicable only if a portal vein resection performed).

Assessment and reporting of margin status should be standardised on pathological reporting to allow comparison between groups of patients (Chandrasegaram et al 2015). The SMA, PV and posterior margins are most frequently involved in R1 resections. Ideally pathologist and surgeon should consult on margins before fixation and inking. If not possible then the surgeon should mark key margins.

Prognostic importance of pancreatic margins

Not all pancreatic margins have equal prognostic significance. A study by Jamieson et al (2010) analysed pancreatic margins by mobilisation margins (anterior and posterior margins) and transection margins (pancreatic transection margin, medial margin and adjacent transection margins). Involvement of mobilisation margins alone was associated with a longer median survival

compared to involvement of the transection margin (median survival 18.9 versus 11.1months; P <0.001). Another study by Delpero et al. (2014) reported that a positive posterior margin had no impact on progression-free survival.

Recommendations

A resection specimen is considered R0 if all surgical margins are clear by ≥1mm. However, regardless of the R status, the microscopic clearance of critical margins, i.e. SMA, pancreatic transection and SMV/PV margins, must be recorded in the pathology report.

Use a structured pathology reporting protocol that standardises the reporting of surgical margin status and relevant issues such as depth of portal vein invasion (RCPA 2014).

Include basic clinical information provided on the request form, the method of specimen handling and all standard pathology elements in the report.

Neo-adjuvant therapy

Although neo-adjuvant therapy has a positive influence on patient survival in other cancers such as breast cancer and rectal cancer, the role it plays in patients with pancreatic adenocarcinoma is unclear.

Some centres in Australia (and internationally) use pre-operative neo-adjuvant therapy – chemotherapy and radiotherapy (RT) – in patients with borderline resectable disease (Heinemann et al 2013).

Some evidence suggests that preoperative neo-adjuvant therapy improves survival outcomes for patients with resectable and borderline resectable pancreatic cancer compared to patients not given treatment or surgery (Gillen et al 2010, Andriulli A et al 2012). Most of these data are retrospective or small prospective series. Interpretation is further complicated by inconsistent definitions of resectability, the introduction of new drugs with greater efficacy in the metastatic setting and the combined use of chemotherapy and RT. All of these confounding issues have resulted in confusion when interpreting patient outcomes involving neo-adjuvant therapy.

Consistency in resection definitions will help clarify the use of neo-adjuvant treatment for this disease.

Neo-adjuvant therapy and resectable disease

This area remains investigational with active research currently being conducted.

The results of the Australian GAP study, which aimed to look at the feasibility of giving pre-operative chemotherapy to patients with resectable pancreatic cancer, indicated that pre-operative treatment (gemcitabine–Abraxane) was safe, did not impair the ability to do surgery and improved the R0 resection rate for patients considered to have resectable disease. The study also showed that post-operative chemotherapy was only deliverable in 60% patients whereas pre-operative treatment was given to 93% of patients (ASCO 2015 Abstract). Other regimens have also been explored in this resectable setting including Folfirinox and single agent gemcitabine.

Theoretically, the use of neo-adjuvant therapy before surgery in patients with resectable disease is likely to translate into more patients receiving treatment because patients do not tolerate treatment as well post-operatively. In addition, patients who recover well post-operatively but had no pathological response could be given a different treatment after surgery; however, the impact of this approach on ultimate outcome remains investigational.

Similarly, pre-operative RT for resectable patients remains an area of ongoing research. RT can cause toxicity (e.g. duodenum) and can be difficult to complete for some patients.

Stents are commonly used to manage biliary or duodenal obstruction in patients with pancreatic adenocarcinoma. Patients with lesions in the pancreatic head may need metal (not narrow plastic) stenting prior to operative intervention or chemotherapy ± RT.

Neo-adjuvant therapy and borderline resectable disease

Currently borderline disease definitions vary, which complicates any recommendations regarding the role of neo-adjuvant therapy in this patient group. Several overviews have suggested benefit for neoadjuvant chemotherapy (Ferrone et al 2015; Gillen et al 2010, Andriulli et al 2012). As stated above, the confounding aspects of current data suggest this remains investigational.

Patient should first be evaluated to confirm their borderline status by an experienced MDT. Once confirmed, patients should be informed that the evidence for neo-adjuvant therapy having a significant impact on resectability or curability remains uncertain. Patients should be offered the opportunity to participate in randomised trials or, if a trial is unavailable, patients should be offered therapy. Offering initial therapy and re-evaluating operability after several cycles is then considered reasonable and may spare some patients ineffective surgery if they rapidly progress.

The choice of chemotherapy or chemoradiation remains unclear. Both FOLFIRINOX and gemcitabine/Abraxane have shown evidence of objective shrinkage of primary tumours in a small number of patients.

The LAP 07 trial involving patients with non-resectable non-metastatic pancreatic cancer showed that adding RT and erlotinib to standard chemotherapy treatment (gemcitabine) gave patients a longer time period without treatment, which may translate into patients having better quality of life. A small group of patients became resectable, some before and some after being given RT/erlotinib. Accordingly, the use of neo-adjuvant therapy (chemotherapy and/or RT) before surgery in patients with borderline resectable disease may lead to down staging to operability for some patients.

Since toxicity from pre-operative RT is much lower than post-operative RT, the panel recommended pre-operative RT be considered when it is likely to be used post-operatively such as for positive margins or in the setting where PV involvement/abutment indicates a poorer prognosis.

In this setting (of chemoradiation) re-imaging of local disease may be unreliable and all patients should be re-evaluated at an MDT regarding likely resectability and the role of a trial of dissection, in the absence of metastatic disease.

Neo-adjuvant therapy and locally advanced disease

Chemoradiation is an option for the management of unresectable locoregional pancreatic cancer, although its use in this population is controversial and some patients are unfit to receive such intensive treatment.
It has mainly been used in selected patients who do not develop metastatic disease during initial chemotherapy. The panel discussed the recently presented preliminary data from the LAP 07 trial and, as noted above, there is uncertainty about the role of chemoradiation and currently it should only be considered following initial chemotherapy in patients with locally advanced disease outside a clinical trial. Occasional patients may be considered appropriate to be reviewed again for surgical resection. There are recent reports of the use of Folfirinox based therapies in highly selected patients with locally advanced cancers, followed by surgical exploration and resection based on disease response (Ferrone et al, 2015). The consensus was that such an approach should only be considered in highly specialised units.

Assessing patients for neo-adjuvant treatment

The following three factors should be considered when assessing patients for neo-adjuvant treatment:

Physiological status – Many patients are older, frailer and may be medically unfit for treatment or have comorbidities that negate them from receiving chemotherapy and/or RT and/or surgery, even if they are clearly resectable. A patient's level of fitness may determine how long they will receive neo-adjuvant treatment or, if they can improve their fitness, treatment may become a consideration.

Biochemical status – CA 19-9, a tumour marker for pancreatic cancer, is useful in initial diagnosis but more useful in measuring effectiveness of treatment over time in patients with pancreatic cancer.

Some panel members said a package of neo-adjuvant treatment followed by surgery should not be considered for patients with resectable disease who have elevated levels of CA 19-9 (>750 U/ml). Rather, the focus should be upon systemic therapy with low likelihood of surgery, others were not concerned about CA 19-9 levels. CA 19-9 may be a marker for occult metastatic disease. In general, patients with resectable or borderline resectable disease after CT imaging and a high CA19-9 should have neoadjuvant therapy and then be restaged, and only proceed to surgery after local extension or metastases have been excluded.

Anatomical status – Using the consensus guidelines for resectability, patients with tumour abutment on the SMA and/or PV (and those who may require PV resection) should be considered for neo-adjuvant treatment. These patients are considered to be at risk of an R1 resection, the aim of giving neo-adjuvant treatment would be to convert them to R0 (because there is some correlation between R0 resection and survival).

Recommendations

Neo-adjuvant therapy is more likely to be delivered than is adjuvant therapy. Accordingly it can be considered for patients able to cope with multimodality therapy who have clearly resectable pancreatic adenocarcinoma. However, its true value remains speculative and this is an ongoing area of research. Patients should be referred for clinical trials whenever possible.

Consider giving neo-adjuvant therapy as a 'first-line treatment (chemotherapy ± radiotherapy) in patients with borderline resectable disease. Both to attempt to improve resectability and to identify patients who progress and avoid ineffective surgery.

Chemotherapy is recommended as initial therapy in the management of patients with unresectable locoregional pancreatic cancer. The value of the addition of radiation after initial chemotherapy remains uncertain.

Patients requiring biliary stents prior to neo-adjuvant chemotherapy should be given metal rather than plastic stents.

Consider patients' physiological (medical fitness), biochemical (carbohydrate antigen 19-9) and anatomical (patients at risk of R1 resection) statuses when assessing for neo-adjuvant treatment.

Multidisciplinary teams

A multidisciplinary team (MDT) is made up of members from different healthcare professions with specialised skills and expertise who collaborate to make treatment recommendations that facilitate quality patient care.

MDT meetings do not involve delivery of care. An MDT is involved in making decisions about diagnosis and staging, resectability, and developing a plan of management in patients for whom disease classification and setting a treatment plan is less clear.

The pancreatic cancer MDT should include a lead person/clinician responsible for the patient to ensure decisions made by the MDT are followed through, specialists with an interest in pancreatic cancer (surgeon, radiologist, pathologist, radiation oncologist, gastroenterologist), allied health professionals, palliative care professional, GP, nurse coordinator, MDT coordinator, and an IT support person.

Panel members recommended that all patients with pancreatic cancer should be presented at an MDT meeting; however, this may not be practical. At minimum, patients presented to an MDT should include:

- newly diagnosed patients who are potentially operable, including patients with borderline and initially locally advanced/unresectable disease
- patients for whom there is diagnostic uncertainty or uncertainty about how to progress management
- patients with oligometastatic disease (e.g. local recurrence after 2 years)
- patients with unusual recurrences.

All patients with metastatic disease should be registered; however, their management may be triaged to an alternative multidisciplinary forum.

Decisions regarding resectability status should be made by consensus at an MDT meeting with reference to appropriate pancreatic imaging including staging.

Complicated cases may require slide review by a pathologist with subspecialty expertise prior to the MDT meeting. A mechanism with which to flag patients with diagnostic uncertainty/important clinical query should be incorporated to facilitate pathologist attendance at MDT meeting.

The outcomes of MDT meetings must be documented. When discussion about a patient has been limited to information available at the meeting; for example, when a recommendation for treatment is made from a review of imaging alone, this should be stated.

A mechanism for keeping track of patients who have been reviewed by an MDT should be undertaken to ensure recommendations were carried out and that a final outcome is known.

Patients who are not reviewed by an MDT should be registered to facilitate clinical trial screening logs.

Guidelines would be useful for MDTs at private hospitals, especially around surgery to prevent misdiagnosis/misoperation; e.g. liver metastases not pancreatic cancer.

MDTs and network arrangements are particularly valuable in regional centres. These networks bring value to discuss patients, especially for borderline cases and for capturing patients. A defined process for entering a patient into an MDT would be useful for regional centres.

Recommendations

Triage patients to identify those who will undergo multidisciplinary review. Patients for whom setting a treatment plan is less clear should be considered at a multidisciplinary team meeting.

Decisions regarding resectability status should be made by consensus at a multidisciplinary team meeting.

Incorporate a mechanism with which to flag patients with diagnostic uncertainty/important clinical query to facilitate pathologist attendance at a multidisciplinary team meeting.

Discuss patients who could join a trial at a multidisciplinary team meeting, if an appropriate trial is running.

Document outcomes of a multidisciplinary team meeting.

Maintain a register of patients reviewed (discussed as well as registered) by a multidisciplinary team.

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