Leading article

Pancreatic malignancies and premalignant lesions: The current role of the surgical pathologist in the diagnosis and management

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Pancreatic cancer (PC) is the most common type of malignancy of the pancreas. Majority of PCs are ductal adenocarcinomas and variants. PC is the 4th leading cause of cancer death in Western countries (1). Approximately 85% of patients present with advanced and unresectable lesions.

In Australia, PC is the 6th highest cause of cancer related deaths with a dismal 5 year survival of 4-6% (2). In spite of advances in imaging technologies in the diagnosis of PC, an unresolved problem has been the lack of an effective screening tool for early detection. Recognized precursor lesions include pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs) and the recently described intraductal tubulopapillary neoplasms (ITPNs). The recent developments in molecular biology, genetics, epigenetics and proteomics have opened the horizons to detect premalignant lesions and predict their prognosis and risk of malignant transformation.

A diagnosis of PC in a solid pancreatic mass has a very significant clinical impact. Less commonly, a variety of benign processes present as a solid mass and mimic PC, chronic pancreatitis being the most common. One special type of chronic pancreatitis is lymphoplasmacytic sclerosing pancreatitis, also known as autoimmune pancreatitis (AIP). Other neoplasms that can present as a mass lesion include acinar cell carcinomas, pancreatoblastomas, solid-pseudopapillary neoplasms (SPPN), pancreatic neuroendocrine neoplasms (PANNET) and metastatic malignancies.

Carcinomas arising in association with IPMNs and MCNs need to be distinguished from pancreatic ductal adenocarcinomas as the former may have a better prognosis. Careful gross examination with special emphasis on cystic areas is important to make this distinction in resection specimens. Well differentiated PC

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need to be distinguished from pancreatic intraepithelial neoplasia (PanIN). Less frequently other epithelial neoplasms of exocrine origin such as serous neoplasms and a variety of non-epithelial neoplasms may be encountered.

In the setting of a pancreatic resection, peri-ampullary/ampullary and intrapancreatic bile duct carcinomas need to be distinguished from primary pancreatic carcinomas. Advances in minimally invasive and non-invasive procedures have resulted in identification of premalignant lesions and low grade malignancies, and possible detection of PCs at an early stage. Pre-treatment assessment of neoplasms is necessary for the diagnosis, management and prognosis. The combination of the knowledge of the age, solid or cystic nature of the lesion and its location often gives a lead to the diagnosis.

Currently surgical pathologists play a pivotal role in the management of mass lesions in the pancreas by providing both cytological and histological assessment. There are two important advances in this area that requires the expertise of the surgical pathologist.

1. Pre-treatment diagnosis of pancreatic lesions on material obtained by advanced radiological techniques, in particular endoscopic ultrasound examination (EUS) is often requested. Cytological samples are commonly obtained and handling these is a challenge.

2. Increased recognition of the need to differentiate ampullary, distal common bile duct and exocrine and endocrine pancreatic malignancies in resections is a challenge but is important as staging systems are different in each of these tumours. The related issues have been highlighted recently (3,4). The 7th edition of the AJCC Cancer staging manual has updated the staging criteria for extra hepatic bile duct carcinomas by dividing them into distal and proximal (perihilar) based on the location (5). Additionally enhanced knowledge of pathology and behaviour of established entities and emerging entities pose further demands for interpretation.

This article will focus on issues related to the above.

EUS guided sampling of pancreatic lesions:

Cytology is the mainstay while Tru-Cut biopsies are less commonly used for pre-treatment pathological diagnosis.

Cytological assessment

Pancreatobilliary cytology is one of the most challenging areas in cytopathology practice, popularly known as the “tiger territory". Both false-negative and false-positive diagnoses carry grave consequences. Cytological samples are now routinely obtained via EUS than CT guid-

ance and the former is considered superior in many aspects (6).

Current challenges are related to special tumour types (i.e. mucinous and cystic neoplasms, IPMNs), reactive changes of the native pancreaticobiliary epithelium, low grade appearance of some widely invasive carcinomas and inherent morphologic heterogeneity in PC. Another unique problem is the contaminant epithelium and mucin that are picked up during the EUS procedure posing special interpretative problems with regards to the diagnosis of neoplasms.

Strong indications for EUS are the presence of focal lesions (solid and cystic) in the pancreas, dilated pancreatic ducts and bile ducts and recurrent pancreatitis. EUS is used for diagnosis and staging of tumours and tissue acquisition. EUS features cannot distinguish malignant infiltrates, stroma or inflammation with certainty; hence distinction of disease processes that form mass lesions such as PC, chronic pancreatitis, autoimmune pancreatitis and PAN-NETs is not perfected by EUS examination alone. Examination of EUS guided cytology or tissue samples is invaluable to confirm pancreatic carcinoma that frequently present as a solid mass lesion.

The most common EUS sample is a fine needle aspiration (FNA) and less commonly brush samples. Many institutions including ours prefer cytology samples to core biopsies. EUS FNA Cytology assessment of pancreatic lesions has shown a very high degree of accuracy (7-10). Analysis of fluid aspirated from cystic lesions has markedly improved the diagnostic accuracy of mucinous cystic neoplastic lesions (11-14).

The final pre-treatment diagnosis involves a team of clinicians, radiologists, pathologists and scientists. Rapid on site evaluation (ROSE) in the presence of a pathologist or a cyto-scientist is invaluable for immediate feedback of success of the procedure and triaging (15). Real time telecytopathology has been used with success for ROSE. ROSE is of limited value for cystic lesions except for those with a solid component or mural nodule (13). Cyst fluid samples need to be handled differently to samples obtained from solid lesions.

Handling of material obtained at EUS

1. Solid lesions: ROSE is performed in many institutions and a lesion is confirmed. These lesions are often neoplastic. Cell blocks are invaluable for further morphological assessment and ancillary stains. A needle rinse and/or a dedicated pass can be used to prepare a cell block (CB). It is advisable to preserve sufficient material for a CB without making too many smears. If molecular techniques require fresh cells (i.e. lymphoma) the specimen should be triaged

appropriately.

2. Cyst fluid: Gross appearance of the cyst fluid obtained provides invaluable information. Neoplastic mucinous cystic lesions produce thick abnormal mucin resulting in classic radiological and EUS findings. A EUS cyst aspirate that shows the "stranding" sign due to thick, abnormal mucin can be very helpful and may be "diagnostic" of the neoplastic nature of the lesion. Cyst fluid needs to be handled with utmost care especially when the volume is small. In our institution, we have developed a volume based cyst fluid protocol after a validation study (14). We recommend receiving the entire sample in the cytopathology laboratory where triaging for biochemical, cytology and molecular analysis takes place. We have proven that neat fluid as well as supernatant is reliable for biochemical assay and the cell button, supernatant and neat fluid can be used for molecular testing. This approach has proven to be extremely useful for small volumes of cyst fluid (14). Requirements for biochemical analysis may vary according to facilities available such as automated biochemical analysers. Close coordination between the clinical biochemistry and cytopathology team would resolve these practical issues. Cytology preparations have been used for molecular testing with success (14,16,18).

Cytology interpretation

An in-depth knowledge of the anatomy and histology of the melting point of the pancreatico-duodenal-ampullary area is paramount before embarking on assessing EUS samples. The amount of contaminants can be minimised by experienced operators.

Gastric contaminants appear as large flat sheets with oval, round, uniform, evenly placed nuclei with occasional grooves and rare inclusions. An apical mucin cap above the nucleus, pit openings and orderly arrangement of cells characterize gastric contaminants. Additionally gastric contaminants lie in association with thin watery gastric mucin as opposed to thick viscous neoplastic mucin (Fig. 1).

Duodenal contaminants are flat sheets with a starry sky appearance due to goblet cells and may show cells with terminal bar-like border with no cilia (Fig. 2). Other benign cells that are commonly seen in pancreatic aspirates are ductal epithelial cells (Fig.3), acinar and islet cells.

The contaminants and background benign cells need to be differentiated from epithelia of PCs, mucinous epithelium of IPMNs and MCNs. Pancreatic head lesions are generally sampled by transgastric approach while those of the tail and body are sampled transduodenally. Hence care-

ful evaluation of the aspirates with the knowledge of the EUS approach and the site of the lesion is required for accurate evaluation.

Solid lesions:

Most commonly encountered lesions are PC, PAN-NET, SPPN and inflammatory masses.

Pancreatic carcinoma

Most solid lesions are adenocarcinomas, features of which are well illustrated in standard cytopathology texts. The fear factor due to possible consequences of a high risk surgical procedure such as Whipple resection often result in under diagnosis of PC, in particular those that appear cytologically low grade in spite of being biologically aggressive.

Focusing on abnormal cytoarchitecure is vital to detect well differentiated and cytologically bland adenocarcinomas. Mass lesions of PC yield cellular aspirates while the cell yield of mass lesions of chronic pancreatitis and AIP are generally very low. Hence presence of too many “ductal epithelial cells” should raise concern. Malignant epithelial cells usually form 3 dimensional crowded sheets or glands and abnormal configurations. Single cells and bare nuclei with necrosis is the classic malignant background. Malignant epithelium of adenocarcinomas has been given descriptive terms including "drunken honey comb" or "stacked potatoes" in standard cytology texts (Fig. 4). As opposed to this, benign epithelial cells (contaminants or native background cells) appear as bland flat sheets.

The cytoarchitecture and degree of cellularity are very useful features to differentiate morphologically low grade PC from benign ductal epithelium in aspirates. Cytologically low grade gastric or pancreatobiliary type epithelium of PC can closely mimic gastric contaminants; hence knowledge of EUS approach is helpful. Beyond the diagnosis, an attempt at grading and subtyping may be helpful for possible management decisions.

Auto immune pancreatitis (AIP) is a rare benign inflammatory disease of the pancreas that mimics pancreatic malignancy both clinically and radiologically. AIP commonly presents as a diffuse enlargement of the pancreas with diffuse irregular narrowing of the main pancreatic duct. Cytology shows tissue fragments with myofibroblast type cells and infiltrating mononuclear cells. Background inflammatory cells include lymphoplasmacytes. The plasma cells are predominantly IgG4 type that may be confirmed by immunohistochemistry (IHC). Sparse epithelial cells lack atypia. The important clue is the low cellular yield (19). Repeated dry aspirates of

a pancreatic mass when performed by experienced operators should raise the possibility of benign fibrotic or inflammatory lesions such as AIP.

Pancreatic neuroendocrine tumour (PAN-NET)

All PAN-NETs are regarded as at least low grade malignant neoplasms. Again classical cytological features have been well illustrated. Aspirates of PAN-Nets are stroma poor and generally very cellular with the classical neuroendocrine cyto-architecture. Islet cells may be mistaken for low grade PAN-NETs. However, islet cells occur as isolated, tight, organised groups and islands with low nuclear: cytoplasmic ratio and niform acinar arrangements while AN-NETs are classically highly cellular and show cell dispersion.

Neoplastic cells of high grade PAN-NETs appear obviously malignant and commonly show necrosis and mitoses. Cell blocks are invaluable to perform IHC that establishes the diagnosis. PAN-NETs are Pax 8 positive with IHC and this finding is helpful in distinguishing primary pancreatic PAN-NETs from extra pancreatic neuroendocrine tumours (NETs) and paragangliomas, the latter being also positive for S100 by IHC.

Solid pseudopapillary neoplasm (SPPN)

This is another neoplasm that presents as a solid lesion commonly in young females. Cytology shows pseudo papillae with capillaries surrounded by tumour cells that show branching and frond like configurations ("Chinese charterers"). Tumour cells are bland and uniform with grooves and may show intracytoplasmic globules and extracellular metachromatic hyaline globules.

Cystic lesions:

Cystic lesions may be non-neoplastic such as pseudocysts, lymphoepithelial cysts and foregut cysts or neoplastic cysts that include MCNs, IPMNs, or other neoplasms with a cystic component such as cystic PAN-NETs and rare acinar cystadenomas.

The role of the cytopathologist in the management of cystic lesions is to confirm IPMNs, MCNs and other very rare cystic neoplasms differentiating them from chronic pancreatitis with a dilated duct and to assess the degree of dysplasia of the neoplastic epithelium.

In 2012, revised international guidelines for the management of IPMNs and MCNs were formulated (20). It was suggested that all cystic lesions with high risk stigmata should be surgically resected while those with worrisome

features be investigated with EUS FNA. If cytology reveals high grade features again surgery is recommended. These guidelines are mostly based on expert opinion than being evidence based. It is noted that individuals and institutions may have modifications based on their personal experiences.

In cytological evaluation of cyst fluids, attention should be paid to both the background and cellular fragments. If background mucin is detected, neoplastic mucin needs to be differentiated from contaminant mucin of the stomach or the duodenum. Non-neoplastic, contaminant mucin is thin, watery, lacks degenerate cells and debris and is accompanied by large sheets of gastric or duodenal epithelium. Neoplastic mucin is viscid with the stranding sign and appears thick, feathery and is colloid-like. Often it is mixed with degenerate cells and debris and may show psammomatous calcifications. Background material of pseudocysts lacks mucin and shows a brown and turbid fluid with pigment material and histiocytes.

Neoplastic epithelium of mucinous cystic lesions in particular shows varying grades of atypia and can be of intestinal, gastric or pancreatobiliary phenotype. EUS approach should always be considered to differentiate benign contaminants from neoplastic epithelium in particular in the setting of cyst fluid.

While duodenal epithelium is easier to be spotted with its characteristic “starry sky” appearance, low grade neoplastic gastric and pancreaticobiliary type epithelium of IPMN and MCN can closely mimic contaminant gastric mucosa. Conversely, gastric contaminants can be mistaken for low grade gastric phenotype mucinous neoplastic cysts. Contrary to this, intestinal type IPMNs can be reliably diagnosed even when they are low grade by the presence of minimally abnormal intestinal type epithelium in a EUS FNA obtained transgastrically (Fig. 5 and 6).

A cyst fluid sample without cells is not an unsatisfactory or inadequate sample. In this situation finding of raised CEA levels (>192 ng/mL) together with a positive v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation is highly suggestive of a neoplastic mucinous lesions (13,14,16-18,21,22).

Serous cystadenomas classically show low volumes of fluid with sparse cellularity and very low CEA levels with no KRAS mutation (23). Presence of abnormal mucin with or without neoplastic epithelium is indicative of a neoplastic mucinous lesion and cyst fluid should be tested for CEA and KRAS mutation if facilities are available. Hence it is obvious that the final diagnosis of cystic lesions should be based on a morphological and multimodal approach with optimal use of cyst fluid.

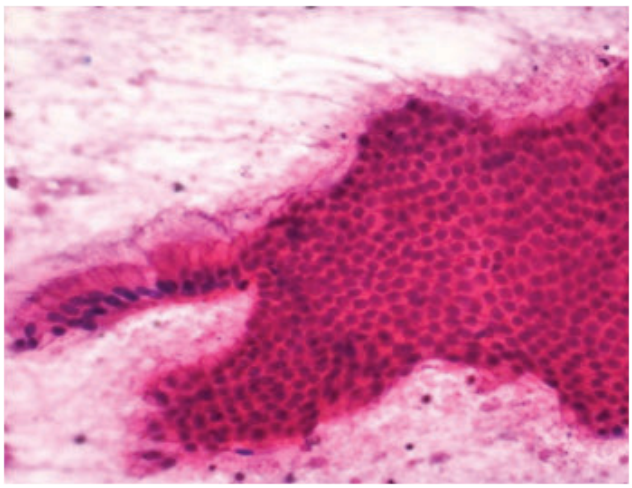

Fig 1: Gastric contaminants: Apical mucin cap above the nucleus, pit openings and orderly arrangement of cells (H & E x200)

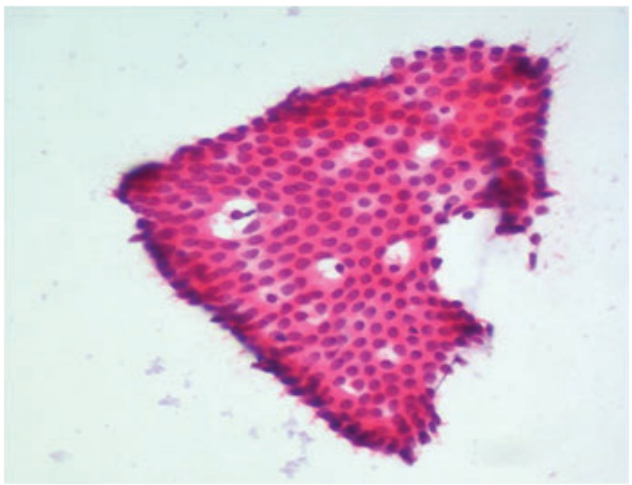

Fig 2: Duodenal contaminants: Flat sheets with A" starry sky" appearance due to goblet cells (H & E x400)

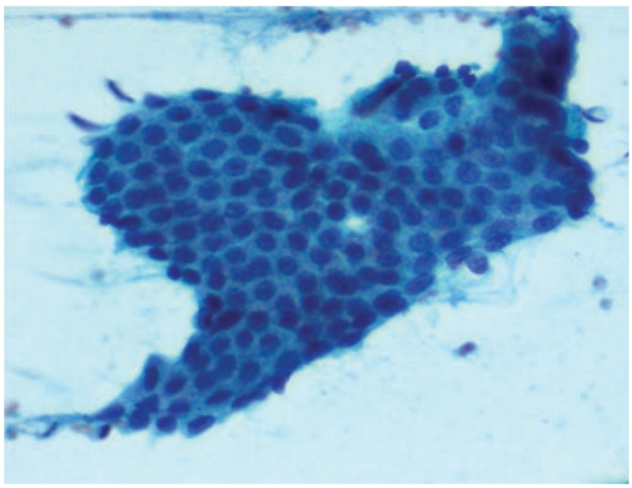

Fig 3: Benign ductal epithelium with uniform bland nuclei. (Pap x 400)

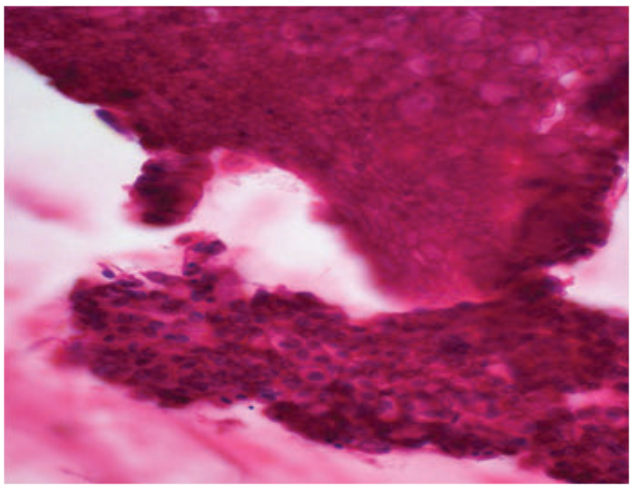

Fig 4: Pancreatic adenocarcinoma: "Drunken Honeycomb" appearance. (H & E x200)

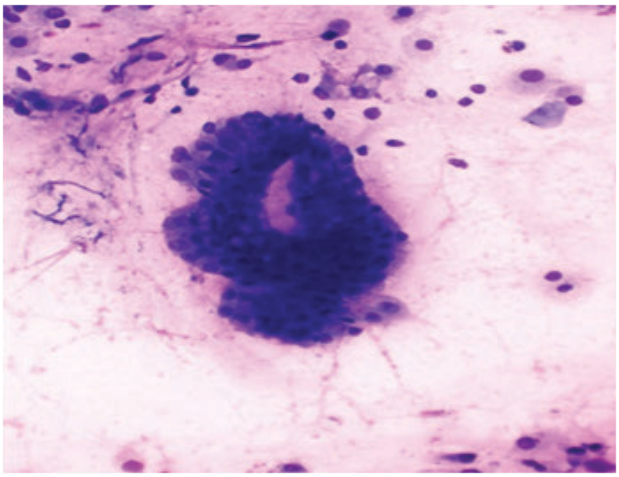

Fig 5: Neoplastic epithelium of IPMN (Gastric type). (Diff quick x 200)

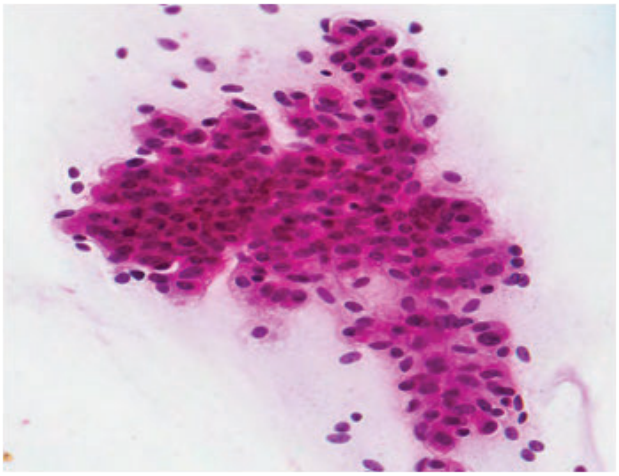

Fig 6: Neoplastic epithelium of IPMN (Intestinal type). (H & E x400)

Histological assessment

Diagnostic features of different types of pancreatic neoplasms including premalignant tumours and cystic neoplasms are well illustrated in text books. New entities and variants have been described and added to the list. Identification of these is required to confer prognosis and influence treatment and management strategies.

Current understanding of early and premalignant lesions and cystic neoplasms is rapidly growing (24-27). Molecular basis of pancreatic carcinoma and other tumours may play a significant role in diagnosis and designing target therapies in the future. The molecular signatures that are linked are KRAS for both IPMN and MCNs, guanine nucleotide protein alpha stimulating (GNAS) mutations for IPMNs but not for MCNs, trypsin for acinar adenocarcinoma, SMAD4 for pancreatic ductal adenocarcinoma, VHL for serous cystadenoma and beta catenin for SCPPT.

In resections that are performed with the intent of cure, some important features that are crucial for prognosis and further management should be included. They are tumour type, size and grade, resection margin status and nodal status. Status of invasion into large vessels and adjacent organs, grade (mitoses and proliferation index), necrosis and metastases are important for prognostication of endocrine tumours.

Standard or structured reports have been developed with the aim of ensuring a complete pathology report that provides key information for many cancers (28-31). Additionally, standard reports in general serve as important vehicles for teaching and collecting data for research. The key to a satisfactory report is optimal gross examination, dissection and sampling in addition to microscopic evaluation (Table 1)

Gross examination and dissection

Techniques and protocols for gross examination of pancreatic resection in particular Whipple resections have been developed by professional societies and organisations (32-36). Standard pancreaticoduodenectomy specimen has been known as the Whipple specimen. These specimens may contain neoplasm of the pancreatic head, ampulla of Vater, duodenum and the distal common bile duct. The specimens usually include the distal stomach, proximal duodenum including the ampulla of Vater, head and neck of the pancreas and the distal common bile duct.

Evaluation of the status of standard margins as well as those specifically requested by the surgeon is crucial. Standard margins documented are pancreatic (neck/body/tail), uncinate (superior mesenteric artery), posterior pancreatic, portal vein bed, bile duct and proximal intestinal or gastric and distal intestinal margins. Distal and partial pancreatectomy specimens are simple to handle and standard grossing approaches are used. Specimens are best received fresh without delay. Often frozen section diagnosis is required for pancreatic neck and/or distal bile duct margins. Specimens arrive in the laboratory with key orientation sutures or are identified on site with the help of the members of the clinical team.

Gross examination starts with orientation of the proximal and distal gastric and, duodenal resection margins and positioning the duodenal C that will identify the pancreatic head. The important uncinate margin should be identified by its caudal and dorsal extension from the main pancreas. The smooth groove created by the superior mesenteric artery and the vein that lies between the neck and the body and the uncinate process is easily identified even in sections (Fig.7).

It is important to identify the common bile duct by its typical tubular appearance and the bile stained mucosa. Distal pancreatic margin is easily identified and often subjected to frozen section examination. Once the key demarcations are identified it is standard practice to ink the specimen to facilitate assessment of relevant margins at microscopic examination (Fig. 7).

Generally, prior to inking the specimen is opened, starting from the stomach along the lesser curvature and antimesenteric border or the opposite aspect to the tumour whilst avoiding cutting through the duodenal papillae. Leaving the duodenal papillae intact facilitates assessment of tumour origin. Once the specimen is inked, margins such as proximal and distal gastric/enteric margins, pancreatic neck resection margin with the pancreatic duct and the common bile duct margins are sampled. Uncinate margin(s) and posterior and anterior margins needs to be sampled but it is more logical to obtain these margins after evaluating the cut slices that show the relationship of the tumour and the inked margins better (Fig. 7)

If the neoplasm is not externally evident, palpation of the pancreas may help to locate the tumour. Common bile duct and/or the pancreatic duct should be probed gently (Fig. 8). In our institution we routinely open the common bile duct (CBD) in resections that are pre-operatively diagnosed as neoplasms of the head of the pancreas, distal common bile duct, and ampulla or periampullary (Fig. 8 & 9). CBD enters the pancreas superiorly and posteriorly and is opened along the posterior surface. We believe that this approach best establishes the gross impression of the origin of the tumour.

Additionally, subtle malignant bile duct strictures and involvement of the CBD by other tumours are best visualised by careful examination of the opened bile duct (Fig.9). Care should be taken to avoid dislodging any tumour while probing and opening the CBD. In cases of suspected IPMNs or MCNs, discretion is used to visualise the relationship of the tumour to the pancreatic duct system (Fig.10). It is important to identify IPMNs of main pancreatic duct and branch ducts separately for prognostication.

Several techniques for gross assessment and sectioning have been described including i) sectioning horizontally along the plane of the main pancreatic duct, ii) sectioning perpendicular to the main pancreatic duct and iii) sectioning perpendicular to the longitudinal axis of the duodenum (32-36). In our institution we section the pancreatic parenchyma perpendicular to the common bile duct to create a series of slices that enable visualization of the tumour and its relevant margins that are already inked. The most distal 15mm of the length of the CBD or ampulla is then sliced perpendicular to the ampulla, particularly in tumours that appear to either originate in or involve this area. The average blocks generated from a standard Whipple resection is 25. These blocks would include all relevant inked margins that are closest to the tumour and representative sections for detailed assessment of morphology and other microscopic parameters.

Vital information obtained from comprehensive gross examination with proper sampling cannot be supplemented by subsequent microscopic examination or ancillary tests. Several studies have shown that introduction of a standardised protocol for macroscopic dissection leads to an increase in the accuracy of reporting both tumour origin and resection margin status advocating a few different techniques (32-35). Tumour origin and resection margin status confer significant differences in survival, staging, adjuvant treatment offered and eligibility for clinical trials.

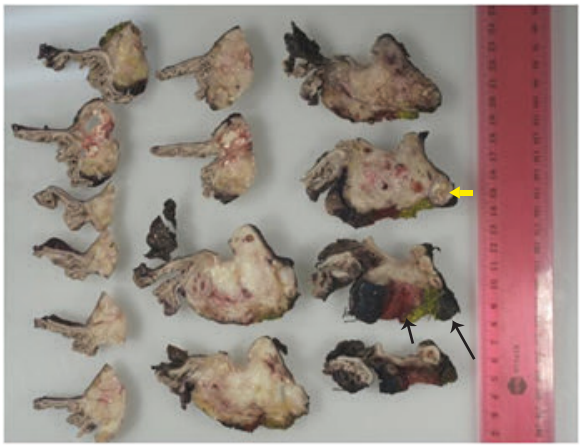

Fig 7: Serial sections with vascular groove (red ink, short arrow), uncinate (yellow ink, long arrow), metastatic nodes (block arrow) in a PC

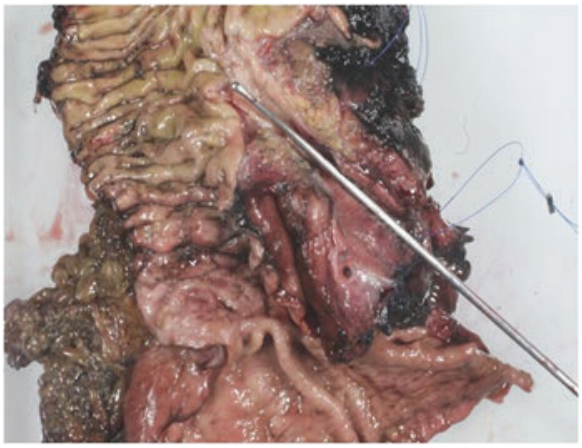

Fig 8: CBD probed and opened

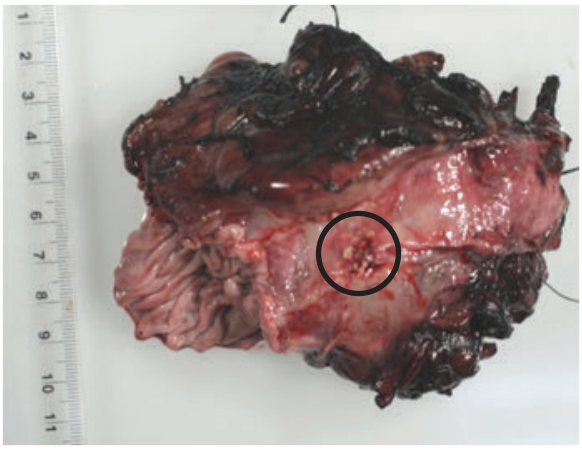

Fig 9: CBD involved by a primary colloid carcinoma

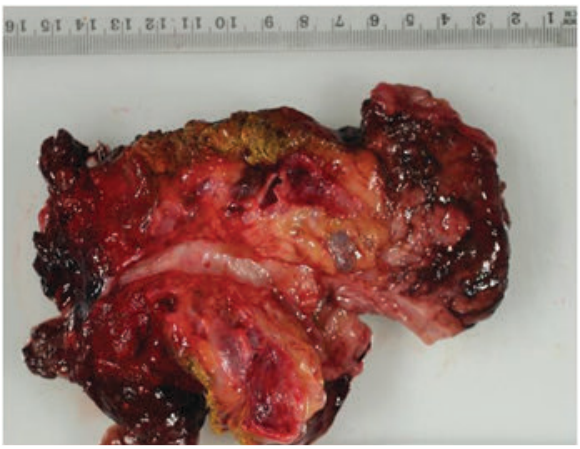

Fig 10: A multicystic branch duct IPMN and largely normal main pancreatic duct

Reporting of pancreatic resections

Table 1 is a guide to standard reporting. A structured report acts as a check list for providing key information that dictates prognostication and further management. The 2010 WHO classification of pancreatic neoplasms has added new entities such as intraductal tubular papillary neoplasms (ITPNNs) and clarified grading and terminology of previously described premalignant lesions and neoplasms such as IPMNs, MCNs and PanIN (37). Such information needs to be incorporated to the report. Although approximately 90% of PC is ductal adenocarcinomas, variants such as colloid (mucinous non cystic carcinomas) and medullary carcinomas are associated with better prognosis while adenosquamous and undifferentiated variants have a better prognosis.

For this reason and for better understanding of biology and development of PC it is important to categorize them appropriately. Colloid carcinomas almost always arise in association with intestinal type IPMNs and are known to have a more favourable prognosis compared to conventional adenocarcinomas.

Table 1: A guide to a standard pathology report with key elements

Macroscopic: Specimen type: Length of duodenum: Length of lesser curve of stomach: Length of greater curve of stomach: Size of gallbladder: Wall thickness of gallbladder, calculi Size & weight of spleen: Length of bile duct: Maximum diameter of bile duct, Location of stent: Size of pancreas: Tumour location: Tumour configuration: Tumour description: Tumour size: Distance of tumour to margins: Pancreatic, uncinate (SMA), posterior pancreatic, portal vein bed, anterior pancreatic capsule, bile duct, proximal intestinal/gastric, distal intestinal. Other findings: Photograph taken: yes/no. Research block taken: yes/no Block key:
Microscopic: Tumour type (WHO): Tumour grade: Extent of invasion: Lymphovascular invasion: Small vessel: (Absent/Suspicious/Present); Large vessel: (Absent/Suspicious/Present). Perineural invasion: (Absent/Suspicious/Present). Perineural invasion of uncinate margin neural plexus: (Absent/Suspicious/Present). Distance of invasive tumour from resection margins: Pancreatic (neck/body/tail) margin: mm. Uncinate (superior mesenteric artery): mm. Posterior pancreatic margin: mm. Portal vein bed: mm. Bile duct: mm. Proximal intestinal/gastric: mm. Distal intestinal: mm. Lymph nodes from the main resection specimen: Total number, Number involved Separately received lymph nodes: Location, Total number, Number involved:

Highest grade of PanIN/dysplasia present:
Grade of PanIN at pancreatic resection margin: Grade of dysplasia at the bile duct/mucosal margin:
Co-existent pancreatic/ductal/small intestinal pathology:
Treatment effect: Not known/No prior treatment/Grade:
Histologically/clinically confirmed distant metastases:
Other comments

Ancillary test findings:
CK7, CK20, CDX2, MUC2, MUC5AC, MUC6
Interpretation of immunohistochemistry: Pancreaticobiliary/intestinal/gastric phenotype

Frozen section (FS) diagnosis and intraoperative margin assessment:

The current role of FS in the management of pancreatic carcinoma has changed over the decades from one that was mostly used for an intraoperative diagnosis to confirm a presumptive diagnosis of malignancy to one that is commonly used for intraoperative consultation to assess the status of resection margins in resection specimens with a pre-operative diagnosis of malignancy. Pre-operative cytological assessment has greatly replaced the need for intraoperative frozen section as a means of primary diagnosis in many tertiary care institutions with strong cytopathology services.

Diagnostic challenges for a primary diagnosis of carcinoma in frozen sections have been well illustrated in many text books repeatedly. Assessment of margin status is a different challenge. If the margins are positive for carcinoma or high grade dysplasia resection may be advanced. A diagnostic challenge is the distinction of involvement of a small duct by residual IPMN from a PanIN lesion; however irrespective of the entity, only the presence of high grade dysplasia will require further margin resection.

Frozen sections are requested from the pancreatic neck and/or distal bile duct margin depending on pre-operative assessment of the lesions. Sections should be obtained after the specimen is orientated with a clear macroscopic impression of tumour distance to the relevant

frozen section margins.

Fresh tissue may be obtained for research purposes for ethically appropriate research. It is clear that the role of the surgical pathologist is vital for clinically relevant management decisions of mass lesions in the pancreas. The demand for expertise and dedication in cytological and histological assessment as well as molecular genetics is rapidly increasing.

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