Guidelines for adequate histopathological reporting of pancreatic ductal adenocarcinoma resection specimens

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Introduction

More than 90% of all malignant tumours of the pancreas are exocrine carcinomas and, of these, 95% are ductal adenocarcinomas (1-2). Since a cure is possible only in case of complete resection of the primary tumour, including its local and regional extensions, the arrival of a resected pancreas in the surgical pathology laboratory is a quite common but for many pathologists stressful event, due to the complexity of the anatomy and the importance of a good dissection in establishing the correct diagnosis and staging. However, a simple, logical approach to the dissection and histopathological reporting can avoid many problems.

Dissection of the pancreatic carcinoma resection specimen

The pancreas consists of the head, the body and the tail. Tumours of the head of the pancreas are those arising to the right of the left border of the superior mesenteric vein. The uncinate process is considered as part of the head. Tumours of the body are those arising between the left border of the superior mesenteric vein and left border of the aorta. Tumours of the tail are those arising between the left border of the aorta and the hilum of the spleen. 60-70% of pancreatic ductal adenocarcinomas are found in the head of the pancreas, especially the upper half, less so in the uncinate process.

Pancreaticoduodenectomy (Whipple procedure) and pylorus-saving pancreaticoduodenectomy

The pancreaticoduodenectomy (Whipple procedure) has emerged as an effective treatment for neoplasms of the four basic components of the resection specimen : head of the pancreas, duodenum, distal common bile duct and ampulla of Vater. The classical Whipple procedure includes wide *en bloc* resection of these components together with the distal stomach ; in pylorus-saving pancreaticoduodenectomy an intact gastric reservoir is preserved. All components of the resection specimen should be measured, and the surface of the pancreas and the proximal (duodenal or gastric) and distal duodenal margins inked. It is advisable to start the dissection, after having fixed the resection specimen overnight in formalin, by opening the duodenum and, in classical Whipple procedure, the distal stomach along the side opposite the pancreas. Any duodenal and gastric masses or ulcers must be documented. Before cutting the specimen any further, sections of the margins, including a shave section of the pancreatic neck margin, a shave section of the bile duct margin, a perpendicular section of the uncinate margin to include the vascular groove, a perpendicular section from the proximal duodenal or gastric margin and a shave section from the distal duodenal margin must be submitted. After this, the common bile duct can be opened to note any strictures or exophytic masses in this duct or the ampulla of Vater.

After the duodenum and the common bile duct have been opened, the pancreas can be sectioned in order to answer four questions :

- Is a neoplasm present ? Tumours with a diameter less than 2 cm are infrequent (3) and may be difficult to recognize by gross inspection.
- If a tumour is present, where is it located, and what is its probable site of origin ? This site is important for adequate staging ; carcinomas of the ampulla of Vater and the head of the pancreas are different with regard to the TNM staging.
- What is the size of the tumour ?
- How many lymph nodes are present ?

The common bile duct can be painted since it might be almost impossible to distinguish the bile duct from the pancreatic duct microscopically. For histological examination, we submit sections of the pancreatic parenchyma, the bile duct, the duodenum, the ampulla, and representative sections of all masses. Particularly helpful is a section parallel to the long axis of the bile duct that includes the duodenum, ampulla, bile duct and pancreas all in one. Sections that demonstrate the relationship of the mass to each of the four basic components of the resection specimen and to the soft tissue margins are a must. All lymph nodes must be embedded for adequate staging.

Distal pancreatectomy

Since the anatomy is simple and there are fewer margins to sample, distal pancreatectomies are easier to handle. After having measured the specimen, a shave section of the proximal pancreatic margin must be submitted. The surface of the pancreas should then be inked,

before making slices perpendicular to the long axis. Representative sections of any tumours are needed, together with all lymph nodes.

Histopathological reporting of pancreatic ductal adenocarcinoma resection specimens

The final report of the pathologist should document

- the grade of the tumour
- the type of the tumour
- the size of the tumour
- the status of the margins
- any lymph node metastases
- presence or absence of vascular and perineural invasion
- presence or absence of peripancreatic tissue invasion
- presence or absence of distal spread

For grading the tumour, glandular differentiation, mucin production, number of mitoses and nuclear atypia are taken into account (4). Most ductal carcinomas are well to moderately differentiated, showing glandular and tubular structures of variable shape, embedded in a desmoplastic stroma. Compared with well differentiated carcinomas, in the moderately differentiated type there is a greater variation in nuclear size and chromatin structure, and less mucin production ; moreover, this type contains more prominent nucleoli. Poorly differentiated ductal carcinomas, composed of densely packed, small irregular glands with abortive mucin production and solid tumour cell sheets and nests with large numbers of mitoses (4), are infrequent. There is a correlation between tumour grade and survival, and grade is an independent prognostic variable (4,5).

Concerning the type of the ductal adenocarcinoma, the following histological variants of the classical ductal adenocarcinoma of the pancreas can be distinguished :

- mucinous non-cystic carcinoma (colloid or gelatinous carcinoma) : relative frequency 1-3%. Mucin accounts for more than 50% of the tumour. It is important to know that the invasive component of some of the intraductal papillary-mucinous tumours resembles mucinous non-cystic carcinoma.
- signet ring cell carcinoma : extremely rare. A gastric primary tumour should always be excluded before making this diagnosis.
- adenosquamous carcinoma : relative frequency 3-4%. The squamous component should account for at least 30% of the tumour mass. In addition, there may be anaplastic and spindle cell foci. Pure squamous carcinomas are very rare.
- undifferentiated (anaplastic) carcinoma.
- undifferentiated carcinoma with osteoclast-like giant cells : rare. This tumour is composed of pleomorphic to spindle-shaped neoplastic cells and non-neoplastic osteoclast-like giant cells. These cells are usually concentrated near areas of haemorrhage and may contain haemosiderin and occasionally phagocytosed mononuclear cells. Osteoid may also be found.
- mixed ductal-endocrine carcinoma (mixed carcinoid-adenocarcinoma, mucinous carcinoid tumour, mixed exocrine-endocrine tumour) : extremely rare. By definition the endocrine cells should comprise at least 1/3 of the tumour. It must be kept in mind, however, that 5% of exocrine carcinomas are non-ductal neoplasms, spanning a wide range of histological features that need to be recognized by pathologists as several entities associated with distinct opportunities for therapy.

The size of the tumour is an independent prognostic factor (6). Japanese collective statistics revealed a 5-year survival rate of 37% for small (less than 2 cm in diameter) carcinomas (7), whereas the current overall 5-year survival rates remain at less than 5% (8). Tumours limited to the pancreas, 2 cm or less in greatest dimension are identified as T1 in the sixth edition of TNM classification (9).Tumours limited to pancreas, more than 2 cm in greatest dimension are T2 tumours. T3 indicates extension beyond the pancreas, but without involvement of coeliac axis or superior mesenteric artery. Finally, T4 does indicate that the coeliac axis or superior mesenteric artery is involved.

Microscopic resection margin involvement has independent prognostic significance to survival (10,11). The section margins that should be examined are mentioned above ; since a common site of recurrence is the tissue surrounding the large mesenteric vessels, the uncinate margin is of major importance.

It is not clear whether regional lymph node metastases significantly worsen the prognosis ; results of studies on this subject are conflicting (6,12-14). For adequate TNM staging, it is important to know which lymph nodes are considered as regional, and that those nodes are different for head and body or tail of the pancreas (9). The regional peripancreatic nodes may be subdivided as follows :

Superior	Superior to head and body
Inferior	Inferior to head and body
Anterior	Anterior pancreaticoduodenal, pyloric (for tumours of head only), and proximal mesenteric
Posterior	Posterior pancreaticoduodenal, common bile duct, and proximal mesenteric
Splenic	Hilum of spleen and tail of pancreas (for tumours of body and tail only)
Coeliac	(for tumours of head only)

The status of lymph extension is recorded as follows : NX regional lymph nodes cannot be assessed, N0 no regional lymph node metastasis, N1 regional lymph node metastases are present. Histological examination of a regional lymphadenectomy specimen will ordinarily include 10 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met,

classify as pN0 according to the sixth edition of TNM (9). However, the Belgian working group advises to keep on using the previous TNM classification on assessing lymph nodes and to use pNX when insufficient lymph nodes have been assessed.

Vascular and perineural invasion are histopathological variables shown to have a poor prognosis in larger series of pancreatic cancer (5,15,16). Since lymph-vessel invasion has been found in the majority of the cases of pN0 state tumours, it must be considered to be a precursor of lymphogenic metastasis or, in the case of an already manifest regional node positivity, as progressive tumour dissemination into more distant lymphatic regions (5). Perineural invasion is more frequently seen in pancreatic carcinomas than in other abdominal tumours, and has sometimes been designated a phenomenon typical for pancreatic carcinoma.

The most frequent direct extension beyond the pancreas involves the retroperitoneal fat (retroperitoneal soft tissue or retroperitoneal space). This dorsal extension is the most frequent reason for locally incomplete tumour resection (17). The survival time of patients with a ductal adenocarcinoma invading the retroperitoneal fat is 6-15 months (13).

Distant spread (pM1) occurs primarily to the liver (17). Other sites, including lungs and bones, can also be involved.

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CHECKLIST PANCREATIC DUCTAL ADENOCARCINOMA
Pathological report

Patient's name:
Given name:
Date of birth:

Registration number:
Hospital/Laboratory:
Preoperative treatment:

Type of intervention
☐ Whipple resection ☐ Pylorus-saving Whipple resection ☐ Distal pancreatectomy

MACROSCOPIC EXAMINATION
☐ specimen not fixed ☐ fixed

Tumour size
Greatest diameter ≤ 2 cm ☐ or > 2 cm ☐

Direct extension
☐ tumour does not extend into adjacent structures
tumour extends into following structures:
☐ retroperitoneal fat
☐ duodenal wall
☐ duodenal mucosa
☐ common bile duct
☐ coeliac axis or superior mesenteric artery
☐

Vascular invasion
☐ not identified
☐ present
☐

Perineural invasion
☐ not identified
☐ present
☐

Surgical margins
☐ all free from tumour
Tumour involves following surgical margins:
☐ pancreatic neck
☐ proximal duodenal or gastric
☐ distal duodenal
☐ bile duct
☐ peripancreatic extension at the uncinate margin
☐ all other margins free from tumour

Non-neoplastic pancreas
☐ unremarkable
Following abnormalities present
☐ focal chronic pancreatitis
☐ extensive chronic pancreatitis
☐ fibrosis
☐ acute pancreatitis
☐ islet cell hyperplasia
☐

HISTOLOGIC EXAMINATION

☐ no residual carcinoma

Tumour type
☐ adenocarcinoma
☐ mucinous non-cystic carcinoma
☐ signet ring carcinoma
☐ adenosquamous carcinoma
☐ undifferentiated carcinoma
☐ undifferentiated carcinoma with osteoclast-like giant cells
☐ mixed ductal-endocrine carcinoma
☐

Tumour location
☐ pancreas head
☐ pancreas body
☐ pancreas tail
☐ pancreas

Histological grade
☐ well differentiated
☐ moderately differentiated
☐ poorly differentiated/undifferentiated
☐

In situ carcinoma
☐ not identified
☐ also present
☐

Lymph nodes
Number of metastatic nodes in relation to total number of nodes examined
☐ superior:
☐ anterior:
☐ posterior:
☐ inferior:
☐ splenic:
☐ coeliac:
☐ no direct tumour extension into lymph nodes identified
☐ direct tumour extension into lymph nodes is present

CONCLUSIONS

Stage pTNM
☐ Tis ☐ T1 ☐ T2 ☐ T3 ☐ T4
☐ NX ☐ N0 ☐ N1
☐ MX ☐ M1

Signature:

Date:

N.B. Samples of tumour frozen