Carcinoma of the exocrine pancreas: The histology report

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On behalf of the “Gruppo Italiano Patologi Apparato Digerente (GIPAD)” and of the “Società Italiana di Anatomia Patologica e Citopatologia Diagnostica”/International Academy of Pathology, Italian division (SIAPEC/IAP)

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Abstract

The Italian Group of Gastrointestinal Pathologists has named a committee to develop recommendations concerning the surgical pathology report for pancreatic cancer. The committee, formed by individuals with special expertise, wrote the recommendations, which were reviewed and approved by council of the Group. The recommendations are divided into several areas including an informative gross description, gross specimen handling, histopathologic diagnosis, immunohistochemistry, molecular findings, and a checklist. The purpose of these recommendations is to provide a fully informative report for the clinician.

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1. Introduction

Pancreatic ductal adenocarcinoma (DAC) is one of deadliest of all cancers. Few therapies are efficacious and until recently very little was known about the pathogenesis of this disease. In the last twenty years several advances have been registered in the field of pancreatic pathology that permit a better understanding of the biological mechanisms involved in pancreatic cancer (PC) and a better treatment of the patients. These include the identification of some key molecular events in the pathogenesis of DAC [1]. The development of DAC is presumed to be preceded by proliferative intraductal changes, such as pancreatic intraepithelial neoplasia (Pan IN) and these are now well characterized [2]. A number of variants of PC with peculiar genetic and clinical characteristics have been identified [3]. The subtypes and the natural biology of cystic neoplasms of the pancreas including mucinous cystic and intraductal papillary mucinous neoplasms are now better defined, and this is important because cystic neoplasms can be diagnosed and cured before an invasive cancer develops [4]. Finally, it is now evident that PC aggregates in some families and some of the genes responsible for familial aggregation of PC have been identified [5]. We have considered all the above reported advances made in pancreatic pathology with the aim of providing a fully informative pathologic report of PC for the clinician.
2. Epidemiology

DAC and its variants represent the most frequent neoplasm of the pancreas, accounting for 85–90% of all pancreatic neoplasms [6]. The incidence of pancreatic cancer does not vary significantly from country to country [7].

In the year 2000, 217,000 new cases of pancreatic cancer (PC) and 213,000 deaths were reported worldwide, and in Europe 60,139 new patients (10.4% of all digestive tract cancers and 64,801 deaths) were registered [8].

In Italy, during the period from 1998 to 2002, PC ranked 11th and 10th among the most frequent cancers in males (2.2% of all cancers) and females (2.8% of all cancers), respectively. It represented the 7th most frequent cause of cancer death (4.6% of all cancer deaths) among males and the 6th (6.6%) among females. It has been estimated that every year 4,388 and 4,214 new PCs are diagnosed among males and females, respectively. With regard to mortality, in 2002 there were 4,069 deaths due to PC among males and 4,280 among females. The incidence did not vary across Italy and the ratio between areas with highest and lowest rates is about 2 [9].

The median survival of patients with metastatic PC not undergoing active therapy is 3–5 months and 6–10 months for locally advanced disease, which increases to about 11–15 months with resectional surgery [10]. Due to the late presentation and aggressive tumor behavior, only a minority of patients can undergo radical, potentially curative surgery. Major progresses in the last ten years have included improvements in multidisciplinary referral centers and improved survival using systemic chemotherapy [10].


The clinical diagnosis of PC is based on common symptoms that include:

- Pain in the upper abdomen that typically radiates to the back
- Painless jaundice when a cancer of the head obstructs the common bile duct
- Loss of appetite and/or nausea and vomiting
- Severe and rapid weight loss

Trousseau sign due to hypercoagulability with formation of spontaneous thrombosis in the portal blood vessels, the deep veins of extremities or superficial veins anywhere in the body, is sometimes associated with PC.

Liver function tests can show a combination of results suggestive for bile duct obstruction/raised conjugated bilirubin, γ-glutamyl transpeptidase and alkaline phosphatase levels. CA-19-9 (carbohydrate antigen 19.9) is the most commonly used marker for PC and has a sensitivity of 70–90% and specificity of 90% and is better than other markers including CEA, CA-50 and DUPAN-2 [11]. The available diagnostic techniques of transabdominal ultrasound (TUS), computed tomography, endoscopic retrograde cholangio-pancreatography (ERCP), magnetic resonance imaging (MRI) and endoluminal ultrasonography (EUS) are superior to other non surgical screening tests in detecting pancreatic lesions.

In recent analyses of the diagnostic accuracy of various techniques, TUS provided a diagnostic accuracy of 75%, contrast-enhanced multidetector CT scan of 97%, MRI of about the same percentage of CT, and ERCP of 70–82% [11].

4. Pathology [4,6]

4.1. Preoperative pathologic diagnosis

Pathologic verification of tumor diagnosis obtained by imaging and tumor markers is required to avoid unnecessary diagnostic laparotomy and to classify the type of tumor precisely before major surgical pancreatic resection, notorious for its morbidity and mortality. Pathologic evaluation is based on fine-needle cytologic aspirated (FNA), endoscopic brushing cytology and tissue biopsies.

Ultrasound “or” CT guided percutaneous transabdominal FNA cytology has a sensitivity and specificity of 69% and 100%, respectively, for tissue diagnosis [10]. The sensitivity and specificity of EUS with FNA is >90% and 100% respectively, but requires an expert team with the presence of a cytologist evaluating the adequacy of the cytological material [12].

Non traumatic FNA, guided by intraoperative ultrasound, is safer and diagnostically more accurate than intraoperative biopsies, either wedge or large needle. With FNA the direct biopsy risks of hemorrhage, pancreatitis and abscess formation can be avoided and multiple aspirations from different areas can be safely done. Intraoperative FNA provides precise differentiation between chronic pancreatitis and PC in 95–100% of cases [13]. As a consequence FNA is considered the safer and more accurate diagnostic technique for intraoperative evaluation of a pancreatic mass, especially when it is deeply situated in the gland.

In most cases, the aspirated material not only permits recognition of malignant cells, but also allows distinction of adenocarcinomas from endocrine tumors and with the help of immunohistochemistry, identification of different types of exocrine and endocrine tumors (Table 1). Pancreatic neoplasms involving the bile duct can be identified with direct bile duct brushing cytology (Table 2) and this technique has practically substituted bile duct sampling due to its superior sensitivity and specificity [14]. However, brush cytology results in a higher false positive and negative rate when compared to FNA [15].

Table 1

<table>
<thead>
<tr>
<th>Diagnostic features of malignancy in FNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tightly packed small or large clusters of epithelial cells</td>
</tr>
<tr>
<td>Enlarged, irregular nuclei, with prominent nucleoli and loss of nuclear polarity</td>
</tr>
<tr>
<td>Cytoplasm usually scanty</td>
</tr>
<tr>
<td>Occasional mitoses</td>
</tr>
</tbody>
</table>
Table 2
Diagnostic features of malignancy in bile duct brushing cytology

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>High cellularity</td>
</tr>
<tr>
<td>Background necrosis</td>
</tr>
<tr>
<td>Nuclear molding</td>
</tr>
<tr>
<td>Chromatin clumping</td>
</tr>
<tr>
<td>Increased nuclear to cytoplasmic ratio</td>
</tr>
</tbody>
</table>

Table 3
Diagnostic features of malignancy in ductal adenocarcinomas regardless of the type of biopsy

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in the number of glandular structures</td>
</tr>
<tr>
<td>Disorganized duct distribution</td>
</tr>
<tr>
<td>Incomplete glandular lumens</td>
</tr>
<tr>
<td>Necrotic material within glandular lumens</td>
</tr>
<tr>
<td>Variation in nuclear size among ductal cells</td>
</tr>
<tr>
<td>Perineural invasion</td>
</tr>
</tbody>
</table>

All biopsy methods described allow a histodiagnosis (Table 3).

A core needle biopsy can be obtained preoperatively with an 18-gauge needle guided by CT, TUS, EUS, or periope ratively with a Silverman or similar “thick” needle under the visual control of the surgeon. Wedge biopsy can be obtained perioperatively and is suitable for frozen section diagnosis.

Visually directed biopsies can be obtained preoperatively under laparoscopy, including laparoscopic US, a technique also used to define the extent of the disease and monitor results of treatment [16].

4.2. Gross specimen examination, handling and reporting

4.2.1. Clinical information required

Clinical information that must be given to the pathologist for the examination of specimens removed from patients with carcinoma of the exocrine pancreas:

1. Patient identification
   - Name
   - Birthdate
   - Gender

2. Responsible physician(s)

3. Date of procedure

4. Other clinical information
   (a) Clinical history
      - Jaundice
      - Pancreatitis
      - Diabetes mellitus
      - Familial or inherited cancer
      - Other
   (b) Imaging and endoscopic findings
   (c) Clinical diagnosis
   (d) Specific procedure (FNA, brushing, needle biopsy, wedge biopsy, partial pancreatectomy, Whipple procedure)
   (e) Operative finding
   (f) Anatomic site(s) of specimen

4.2.2. Dissection and reporting of pancreatic resection specimens

Type of specimen and organs present in specimen

The type of specimen should be indicated, e.g. standard Whipple pancreaticoduodenectomy (PD), a pylorus-sparing PD, a total PD, a left (or distal) pancreatectomy.

The Whipple’s procedure consists of partial pancreatectomy plus distal gastrectomy and duodenectomy. The gallbladder is also usually resected during the operation and may be added to the specimen or submitted separately. The distal stomach is not resected in pylorus-preserving PD (Figs. 1 and 2). The total PD also comprises the body and tail of pancreas with or without the spleen and/or stomach. In the left (or distal) pancreatectomy only the body and tail of pancreas, with or without the spleen are present (Fig. 3).

Specimen handling and gross examination. PD specimens should be examined in the fresh, unfixed state (this is less important for the left side resections), possibly in close cooperation with the surgeons.

Fig. 1. Resection margins in a pancreatic specimen from pylorus-sparing pancreaticoduodenectomy. a = duodenal proximal margin; b = cystic duct margin; c = common bile duct margin; d = pancreatic parenchymal margin (with main duct); e = duodenal distal margin; f = anterior margin; g = medial margin (mesenteric groove margin); h = posterior margin.

Fig. 2. Resection margins in a pancreatic specimen from pylorus-sparing pancreaticoduodenectomy (transversal section). a = anterior margin; b = medial margin (mesenteric groove); c = posterior margin; d = duodenum; e = papilla of Vater.
The common bile duct and the main pancreatic duct should be probed, and the whole specimen cut horizontally along the probes. The site of origin of the neoplasm must be precisely identified, in order to exclude ampullary carcinomas, since the latter have a significantly better prognosis [17]. The neoplasms involving pancreatic head should be identified as follows:

1. Pancreatic tumor: a neoplasm localized in the pancreatic head
2. Ampullary tumor: a neoplasm centered in the ampulla
3. Periampullary tumor: a neoplasm in an advanced stage for which the precise site of origin is not identifiable
4. Terminal bile duct tumor: a neoplasm located in the lower third of the common bile duct.

The site of the tumor should therefore be reported in relation to the ampulla and common bile duct, and the distance from each should be measured.

Invasion of adjacent structures (duodenum, extrapancreatic duct, peripancreatic soft tissue) should be reported and the tumor size should be measured in at least two dimensions. Tumor size is an independent prognostic factor in most studies [18]. Features such a cyst formations, intraductal tumor growth and the presence of mucus within dilated ducts should be reported, these features being characteristic of particular types of pancreatic tumors generally associated with a favorable prognosis, including mucinous cystic tumors [19] and intraductal papillary mucinous tumor [20].

Left pancreatectomy is the treatment of choice for pancreatic tumors of the body and tail. The size of the tumor and its distance from the parenchymal resection margin should be measured and any invasion of the peripancreatic tissue noted. Macroscopic features, in particular cyst formation or a solid appearing tumor with smooth outlines need to be recorded, since they are indicators of special tumor types, such as mucinuous cystic tumors and solid-pseudopapillary tumors.

For cystic tumors, the cyst content (mucoid, serous, bloody, necrotic), the unilocular or multilocular aspect, the internal surface (smooth or papillary), the presence of mural nodules, and the communication with larger pancreatic ducts should be reported. In these cases the sampling should be extensive, in order to find a possible infiltrative focus.

**Resection margins.** Completeness of resection should be assessed by gross examination and confirmed by histological examination [21–23].

Resection margins include the common bile duct margin, the pancreatic transection margin (with main pancreatic duct), the duodenal transection margin (Fig. 1). Both the common bile duct and the pancreatic transection margins should be evaluated intraoperatively on frozen sections (en face).

Most important is the circumferential resection margin. It is defined as the anterior, medial and posterior dissection margin on peripancreatic adipose tissue behind the head of the pancreas; in particular, the medial dissection margin is located dorsal and lateral to the superior mesenteric artery, usually has a shallow groove shape (“mesenteric groove”), and must be carefully examined in order to find a possible neoplastic infiltration (Figs. 1 and 2). It is important to consider also the serosal lining of the anterior pancreatic surface, in order to exclude a serosal neoplastic diffusion.

In left pancreatectomy the circumferential margin on peripancreatic adipose tissue and the transection margin toward the corpus has to be considered (Figs. 3 and 4). The transection margin should be evaluated intraoperatively on frozen sections.

All resection margins should be painted with India ink and should be sampled. The tissue of each resection margin should be sectioned perpendicularly to the surface and successive, numbered specimens should be submitted for histological examination. Blocks are taken from the pancreatic parenchyma, sectioned at 2 mm intervals in a bread loaf fashion using a sharp blade, to evaluate the relationship between tumor and resection margins, duodenum and ampulla of Vater, tumor-free parenchyma and other organs [24].
**Lymph node examination.** The removed lymph nodes should be classified and numbered, for daily routine assessment, according to the TNM system [25]. The regional lymph nodes for the pancreas can be grouped into anterior pancreaticoduodenal, posterior pancreaticoduodenal, inferior (including lymph nodes surrounding the superior mesenteric vessels), bile duct, infrapyloric (for tumors of the head of pancreas) and superior [26]. A carefully sampling of the lymph nodes must be performed, since lymph node status is an important prognostic factor [27,28]. In our experience, an integral sampling of the peripancreatic adipose tissue is mandatory to perform a complete analysis of all lymph nodes, because, frequently, they often are very small and cannot be easily separated from peripancreatic fibrofatty tissue: in PD specimens, lymph nodes often sit in the groove created by the junction of the pancreas and the bowel wall; in distal pancreatectomy they almost locate into the fatty perivascular tissue.

All nodes should be separately submitted for histological examination, and nodes with a diameter >1 cm should be hemisectioned.

**Microscopic examination.** All tissues should be embedded in paraffin, sectioned and stained with H&E. A section from the tumor specimen should additionally be stained with PAS; optional stains include Elastica van Gieson for vessel segments or various immunostains (CK7, 8, 18, 19, MUC1, MUC3, MUC4, MUC5AC, CEA, CA19-9, CA125, DUPAN2, mesothelin, prostate stem cell antigen (PSCA), claudin4, loss of DPC4, p16, p53).

**Histological tumor typing and grading.** Histological tumor typing should be performed according to the generally accepted principles of the WHO [29] (Table 4).

Although more than 90% of the carcinomas are DACs (including its varieties), other malignancies such as acinar or endocrine carcinomas have to be considered. They must be distinguished from secondary metastatic tumors or mesenchymal malignant neoplasms.

As previously mentioned, the most important differential diagnosis is that from ampullary carcinomas. An ampullary origin can be unequivocally established in small lesions by applying strict topographical criteria during the gross and histological examination. The presence of “preinvasive” (adenomatous) modifications in the anatomical structures of the ampulla and the intestinal type of the carcinoma can help in the distinction [17,30].

It is especially important to identify mucinous-cystic tumors and intraductal-papillary tumors because of their incomparably better prognosis.

The “cystic” variant of DAC, due either to degenerative changes or to ectatic changes of the duct system, can mimic the former two neoplasms.

For DACs the grade is an essential and independent prognostic factor and should be recorded according to the criteria of the WHO [6] (Table 5).

**Local invasion.** TNM staging [25] (Table 6) requires to establish if a pancreatic carcinoma has or has not invaded the duodenum, ampulla of Vater, bile duct or peripancreatic tissues (T3) or has invaded the stomach, spleen, colon or adjacent large vessels. Invasion of peripancreatic tissue has been found in up to 90% of cases [21] and indicates a poor prognosis.

**Extent of resection.** Neoplastic involvement of standard surgical margins implicates frequent local recurrence and is associated with a poor prognosis [22]. The posterior margin is more frequently involved than the pancreatic transection margin and bile duct margin [23]; carcinoma less than 1 mm from a margin has to be considered as incompletely excised. The presence or absence of residual carcinoma after surgical resection is a very important prognostic factors and, although not included in the TNM staging, can be indicated by symbol R (see Table 7).

### Table 4
**WHO classification of malignant exocrine pancreatic tumors**

<table>
<thead>
<tr>
<th>Description</th>
<th>SNOMed code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal adenocarcinoma (infiltrating duct carcinoma)</td>
<td>M8500</td>
</tr>
<tr>
<td>Mucinous noncystic carcinoma (mucinous adenocarcinoma)</td>
<td>M8480</td>
</tr>
<tr>
<td>Signet-ring cell carcinoma</td>
<td>M8490</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>M8560</td>
</tr>
<tr>
<td>Undifferentiated (anaplastic) carcinoma</td>
<td>M8020 (M8021)</td>
</tr>
<tr>
<td>Mixed ductal-endocrine carcinoma</td>
<td>M8154</td>
</tr>
<tr>
<td>Osteoclast-like giant cell tumor</td>
<td>M8030</td>
</tr>
<tr>
<td>Serous cystadenocarcinoma</td>
<td>M8441</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>M8470</td>
</tr>
<tr>
<td>Intraductal papillary-mucinous carcinoma</td>
<td>M8503/2</td>
</tr>
<tr>
<td>Invasive papillary-mucinous carcinoma</td>
<td>M8503/3</td>
</tr>
<tr>
<td>Acinar cell carcinoma</td>
<td>M8550</td>
</tr>
<tr>
<td>Pancreatoblastoma</td>
<td>M8971</td>
</tr>
<tr>
<td>Solid-pseudopapillary carcinoma</td>
<td>M8452</td>
</tr>
<tr>
<td>Extremely rare carcinomas</td>
<td></td>
</tr>
<tr>
<td>Clear cell carcinoma (clear cell adenocarcinoma)</td>
<td>M8310</td>
</tr>
<tr>
<td>Oncocytic carcinoma (oxyphilic adenocarcinoma)</td>
<td>M8290</td>
</tr>
<tr>
<td>Choriocarcinoma (NOS)</td>
<td>M9100</td>
</tr>
</tbody>
</table>

### Table 5
**Histological grading of pancreatic ductal adenocarcinoma**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Glandular differentiation</th>
<th>Mucin production</th>
<th>Mitoses (per 10 HPF)</th>
<th>Nuclear features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Well differentiated</td>
<td>Mucin production</td>
<td>Intensive ≤5</td>
<td>Little polymorphism, polar arrangement</td>
</tr>
<tr>
<td>2</td>
<td>Moderately differentiated duct like structures and tubular glands</td>
<td></td>
<td>Irregular 6–10</td>
<td>Moderate polymorphism</td>
</tr>
<tr>
<td>3</td>
<td>Poorly differentiated glands, mucoepidermoid and pleomorphic structures</td>
<td></td>
<td>Abortive &gt;10</td>
<td>Marked polymorphism and Increased size</td>
</tr>
</tbody>
</table>
Factors and corresponding receptors, DNA ploidy or nuclear assess proliferation markers, oncogenes (including growth Other markers. At present the use of special techniques to cause of retroperitoneal local recurrence. Intrapancreatic neural invasion significantly correlates with characteristic histological feature of pancreatic carcinoma. Perineural and intraneural invasion is a arterial or vein is an important negative prognostic factor after mesenteric artery or vein, portal vein and/or common hepatic Vascular invasion. The common DAC is characterized by a proliferation of small to large tubular glands lined by cuboidal to tall cells interspersed in an abundant desmoplastic stroma. The degree of gland formation is proportional to the degree of differentiation, ranging from well formed glands in well differentiated cancer to infiltrating single cells or cells forming solid sheets in poorly differentiated cancers. Near all DACs elicit an intense desmoplastic stromal reaction made of myofibroblast, lymphocytes and inflammatory cells. In well-differentiated DACs, the growth pattern and cytological appearance of the cells may be deceptively benign, closely mimicking non-neoplastic ductules of chronic pancreatitis. However, in well-differentiated DACs malignant glands usually replace the normal lobular arrangement of the acini with haphazardly arranged tubules but, at low magnification, the lobular appearance is generally preserved in chronic pancreatitis and lost in well-differentiated DACs. SMAD4 (DPC4) and TP53 immunolabeling may be a useful tool, when differential diagnosis between regenerative ductular lesions of chronic pancreatitis and DAC should be made, because in the former SMAD4 (DPC4) is never lost and TP53 is negative because it is present in wild form. The cells that line malignant glands typically form a single regular layer, but stratification and irregular papillae may be prominent in some cases. The cytoplasm of tumor cells may be abundant and generally contains different amounts of mucin according to the grade of cancer differentiation. The nuclei may retain basal orientation in well-differentiated DACs but they vary in size, shape, and intracellular location in moderately to poorly differentiated DACs. Histological variants of pancreatic DAC are well documented and included in the 2000 WHO classification. They are adenocarcinoma, undifferentiated (anaplastic) carcinoma, undifferentiated carcinoma with osteoclast-like cells, mucinous non-cystic carcinoma, signet-ring carcinoma, mixed ductal-endocrine carcinoma. Grading is done according WHO grading scheme (Table 5). Pancreatic DAC is an extraordinarily invasive neoplasm growing into and along pancreatic ducts, in some cases mimicking intraepithelial neoplasia (PanIN). Neural invasion is a very common finding as well as the extension to peripancreatic fat tissue where naked glands can be seen. Lymphatic and blood vessel invasion is also a common finding of PC. Invasion of common bile duct, duodenal wall and ampulla of Vater is frequently observed in cancer of the head of the pancreas, also when the tumor size is small. Cystic formation is uncommon in carcinomas of the head of

<table>
<thead>
<tr>
<th>Table 6</th>
<th>AJCC TNM staging of pancreatic carcinoma (2010) [25]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tumor</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ including PanIN3</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to pancreas, 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor limited to pancreas, more than 2 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends beyond the pancreas, without involvement of celiac axis or superior mesenteric artery</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor involves the celiac axis or superior mesenteric artery</td>
</tr>
<tr>
<td><strong>Regional lymph nodes</strong></td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>Distant metastasis</strong></td>
<td></td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis and peritoneal cytologic evidence of cancer</td>
</tr>
</tbody>
</table>

**Lymph node spread.** The total number of nodes should be counted during the histological examination, and the number of metastatic nodes and any perinodal invasion should be noted. Patients with multiple group of metastatic lymph nodes survive significantly longer than those with single group of metastatic lymph nodes. The lymph node ratio, that is the ratio of the number of nodes harboring a metastasis to the total number of nodes examined, is one of the most powerful predictors of survival after surgery [28,32]. Currently, there is no recommendation for the use of immunohistochemistry to detect micrometastases in lymph nodes.

**Vascular invasion.** Invasion of large vessels including superior mesenteric artery or vein, portal vein and/or common hepatic artery or vein is an important negative prognostic factor after resection [21].

**Neural invasion.** Perineural and intraneural invasion is a characteristic histological feature of pancreatic carcinoma. Intrapancreatic neural invasion significantly correlates with extrapancreatic plexus invasion, that represents a major cause of retroperitoneal local recurrence.

**Other markers.** At present the use of special techniques to assess proliferation markers, oncogenes (including growth factors and corresponding receptors), DNA ploidy or nuclear morphometry is not warranted for a minimum dataset. In fact, genetic markers that could be used as prognostic indicators of outcome or used for tailored treatment, as for breast, colon, and lung cancer and some hematological malignancies, are needed, but at the moment no molecular or related immunohistochemical tests are available to make personalized treatment possible.

4.2.3. Histopathologic features of pancreatic ductal adenocarcinoma [4,6]

The common DAC is characterized by a proliferation of small to large tubular glands lined by cuboidal to tall cells interspersed in an abundant desmoplastic stroma. The degree of gland formation is proportional to the degree of differentiation, ranging from well formed glands in well differentiated cancer to infiltrating single cells or cells forming solid sheets in poorly differentiated cancers. Near all DACs elicit an intense desmoplastic stromal reaction made of myofibroblast, lymphocytes and inflammatory cells. In well-differentiated DACs, the growth pattern and cytological appearance of the cells may be deceptively benign, closely mimicking non-neoplastic ductules of chronic pancreatitis. However, in well-differentiated DACs malignant glands usually replace the normal lobular arrangement of the acini with haphazardly arranged tubules but, at low magnification, the lobular appearance is generally preserved in chronic pancreatitis and lost in well-differentiated DACs. SMAD4 (DPC4) and TP53 immunolabeling may be a useful tool, when differential diagnosis between regenerative ductular lesions of chronic pancreatitis and DAC should be made, because in the former SMAD4 (DPC4) is never lost and TP53 is negative because it is present in wild form.

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<table>
<thead>
<tr>
<th>Table 7</th>
<th>Residual tumor after surgical resection, R classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>The absence or presence of residual tumor after surgical resection (designated by the symbol R) is not part of the TNM staging system, but it is clinically important</td>
<td></td>
</tr>
<tr>
<td>RX</td>
<td>Presence of residual tumor cannot be assessed</td>
</tr>
<tr>
<td>R0</td>
<td>No residual microscopic or macroscopic tumor</td>
</tr>
<tr>
<td>R1</td>
<td>Microscopic residual tumor</td>
</tr>
<tr>
<td>R2</td>
<td>Macroscopic residual tumor</td>
</tr>
</tbody>
</table>
the pancreas, but it may be observed in carcinoma of the tail, raising the differential diagnosis with mucinous cystic tumor.

4.2.4. Immunohistochemical findings in pancreatic adenocarcinoma and precursor lesions [4]

Conventional DACs invariably show at least focal mucin positivity by using Alcian Blue stain alone or combined with PAS stain. In addition, stains for cytokeratins (CK) 7, 8, 18, and 19 and epithelial membrane antigen (EMA) are usually positive [4]. CK20 is detected in less than 10% of DACs. CK20 is much more frequently expressed in ampullary adenocarcinoma (of intestinal type but not of pancreato-biliary type), intraductal papillary mucinous neoplasms (IPMNs) of intestinal type, and related colloid adenocarcinoma (mucinous non cystic adenocarcinomas), and in mucinous cystic adenocarcinomas. Non specific markers often detectable in DAC include CA19-9, CEA, CA125, and DUPAN-2. Of these, CEA and CA125 are tumor-associated glycoproteins not expressed in normal ductal cells but observed in low-grade to high-grade pancreatic intraepithelial neoplasia (PanIN). The MUC proteins are variously expressed, in all types of ductal neoplasms. Most conventional DACs express MUC1 (86%), MUC3, MUC4, MUC5AC (71%). About 20% of DACs express MUC6 (a pyloric gland mucin) and only 6% express MUC2. CDX2, like MUC2, is positive in a minority (14%) of usual DACs but is expressed in 100% of colloid carcinoma. MUC2 and CDX2 may be useful in differentiating advanced ampullary carcinoma from DACs of the head of the pancreas especially when the ampullary cancer is of the intestinal type in which CDX2 is found in 100% of the cases [17]. MUC2 and CDX2 are never expressed in low and high grade PanIN; on the contrary a diffuse and strong MUC2 and CDX2 expression is seen in intestinal type IPMN, allowing distinction of these two lesions. Stains for chromogranin or synaptophysin may demonstrate scattered endocrine cell components associated with the neoplastic glands. Diffuse chromogranin or synaptophysin immunostaining raises the possibility of a poorly differentiated endocrine carcinoma or of a mixed endocrine-exocrine cancer. Pancreatic DACs also overexpress growth factors and related receptors such as epidermal growth factor and its receptors c-erbB-2, c-erbB-3, transforming growth factors alpha and beta and their receptors, platelet-derived growth factor (PDGF) A and B and their receptors, and fibroblastic growth factor and its receptor [4].

4.2.5. Precursor lesions [2,4]

Different non-invasive precursor lesions can give rise to invasive adenocarcinoma of the pancreas [2,4]. The early detection of these non-invasive lesions offers the potential to cure early PCs and to reduce cancer mortality. Non-invasive precursors of invasive DAC include one microscopic lesion; pancreatic intraepithelial neoplasia (PanIN), and two mass forming lesions: intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN). Their clinical detection and treatment can interrupt the progression to invasive cancer, and save lives [33].

1. Pancreatic intraepithelial neoplasia (PanIN) [2,4]. PanIN is defined as a microscopic papillary or flat non-invasive epithelial neoplasm arising in the pancreatic ducts. PanINs are characterized by columnar to cuboidal cells with varying amounts of mucin and degrees of cytologic and architectural atypia. PanINs usually involve ducts <5mm in diameter [2,4]. PanIN lesions (including lesions that were formerly called ductal non-papillary or papillary hyperplasia) characteristically occur in intralobular ducts, are not detected macroscopically, and are clinically silent. Early lesions, PanIN-1A and PanIN-1B, show minimal cytological and architectural atypia. PanIN-2 lesions show mild to moderate cytological and architectural atypia with frequent papillary formation. PanIN-3 lesions exhibit severe cytological and architectural atypia. PanIN lesions have been integrated into a tumor progression model for DAC that links the morphological changes in the duct epithelium with genetic alterations. The genetic profile of PanINs show both activation of oncogenes and inactivation of tumor suppressor genes.

Activating point mutations in the KRAS2 gene occur in the lowest grade precursor lesions (PanIN-1), placing them among the earliest genetic events that occur in the development of DAC. Loss of p16 protein expression is seen in <30% of the low-grade PanIN lesions (PanIN-1), in 55% of PanIN-2 lesions, and in 70% of PanIN-3 lesions. Inactivation of the TP53 gene appears to be a relatively late event in the development of pancreatic neoplasia, as it is seen predominantly in high-grade precursor lesions (PanIN-3).

The information regarding the progression of the different types of PanIN lesions is still limited. PanINs-1 and PanINs-2 are of unproved malignant potential and pathologists are asked not to report these in diagnosis. Although the clinical significance of PanIN-3 lesions is not clearly established, they should be recognized and reported in the pathology report.

2. Intraductal papillary-mucinous neoplasms (IPMNs) [4]. IPMNs are characterized by a grossly visible (typically >1.0 cm) intraductal proliferation of columnar mucin-producing cells, arising in the main pancreatic duct or its major branches. The degrees of papillary formation, mucin secretion, duct dilatation (cyst formation), and dysplasia are variable [20]. IPMNs lack the “ovarian-type” hypercellular periductal stroma that characterizes mucinous cystic neoplasms. Non-invasive IPMNs are classified based on the highest degree of cytoarchitectural atypia into three categories: low-grade dysplasia, moderate dysplasia and high-grade dysplasia/carcinoma in-situ [4]. When IPMNs are associated with an invasive carcinoma, it should be separately classified.

They form a heterogeneous group of neoplasms, which can be divided into at least four types on the basis of their morphology and mucin immunophenotype.

1. Gastric type: characteristically found in the branch duct IPMNs. The epithelium lining gastric IPMNs is composed of foveolar-type epithelium, that usually has only low-grade or moderate dysplasia and expresses immunohistochemically MUC5AC, but not MUC1 or MUC2 (only few scattered goblet cells may be present).
2. *Intestinal type:* characterized by main duct involvement, and formation of tall papillae lined by columnar cells with pseudostratified, elongated nuclei, and basophilic cytoplasm with variable amount of apical mucin, reminiscent of colonic villous adenomas. They usually have moderate or high-grade dysplasia and immunostain for MUC2 and CDX2.

3. *Pancreatobiliary type:* it is less frequent than the others, typically involves the main pancreatic duct and is characterized by thin, branching papillae with high-grade dysplasia. Pancreatobiliary-type IPMNs express MUC1 but not MUC2 or CDX2.

4. *Oncocytic type:* it is characterized by the involvement of the main pancreatic duct or its major branches and is composed of papillae lined by 2–5 layers of cuboidal cells with abundant eosinophilic granular cytoplasm. MUC6, the pyloric type mucin, is consistently and diffusely expressed, whereas MUC1, MUC2, MUC5AC and CDX2 are negative or only focally expressed.

While the common MUC2+ intestinal IPMNs can be considered as the precursors of the MUC2+ mucinous noncystic carcinoma, the MUC2−/MUC1+ pancreatobiliary IPMNs appear to have a close relationship to common type DAC (the immunohistochemical mucin expression pattern distinguishes different types of IPMNs of the pancreas and determines their relationship to mucinous noncystic carcinoma and DAC [34]). IPMNs with a colloid type of invasive carcinoma have a better prognosis than do those with a ductal (tubular) type of invasive cancer.

Activating point mutations of KRAS oncogene have been reported in 30–80% of IPMNs, with increased prevalence in high grade IPMNs. Activated PIK3CA gene that is also activated in colloid adenocarcinomas, occurs in some of IPMNs.

3. *Mucinous cystic neoplasms (MCN)* [19]. They affect almost exclusively women, predominantly involve the tail of the pancreas, do not communicate with the ductal system, and are usually accompanied by the characteristic ovarian-type stroma [19,35]. The presence of carcinomatous stromal invasion characterizes the invasive mucinous cystadenocarcinoma. The invasive component usually resembles the common DAC.

As in the development of DACs, the *K-ras* mutations are early events, while *p53* and DPC4 inactivation are relatively late genetic alterations in the progression of noninvasive to invasive MCNs [36,37].

IPMNs frequently harbor activated *PIK3CA* gene that is also activated in colloid adenocarcinomas, a less aggressive pancreatic carcinoma than DACs.

4.2.6. Molecular findings

*Familial pancreatic cancer* [5]. PC is a disease caused by inherited (germline) and acquired (somatic) mutations in cancer-causing genes. Most DACs are sporadic, but PC can be familial in less than 10% of cases [5]. The genetic basis for most (80%) familial cases is unknown. However, the increased risk of PC is well documented in some heritable genetic syndromes, such as hereditary breast cancer syndrome (BRCA2 mutations), familial atypical multiple mole-melanoma (FAMMM) syndrome (p16 mutation), Peutz-Jeghers syndrome (STK11/LKB1 mutations), hereditary chronic pancreatitis (PRSS1 mutations), hereditary nonpolyposis colorectal cancer (HNPPC) syndrome (DNA mismatch repair genes mutations), and Fanconi’s anemia (FANC-C and FANC-G mutations) (Table 8). For patients, with such molecular alterations, a close follow up must be carried out by using EUS and MRI for an early diagnosis of PC [38]. Inherited genetic alterations information can also be used to quantify a person’s risk of developing an extra-pancreatic malignancy, and screening for these malignancies. On the contrary, a screening program for the average risk individual is not recommended (United States Preventive Service Task Force).

Table 8

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene (chromosomal location)</th>
<th>Risk of pancreatic cancer</th>
<th>Risk of other malignancy</th>
<th>Risk of PC by age 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast cancer syndrome</td>
<td>BRC2A mutations 13q12-q13</td>
<td>10x</td>
<td>breast, ovary, prostate</td>
<td>5%</td>
</tr>
<tr>
<td>Familial atypical multiple mole-melanoma</td>
<td>p16/CDKN2A 9p21</td>
<td>30x</td>
<td>melanoma</td>
<td>15%</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>MLH1, MSH2, MSH6, PMS2 genes muts</td>
<td>unknown</td>
<td>gastrointestinal endometrial ovary</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Hereditary chronic pancreatitis</td>
<td>PRSS1 mutations 7q35</td>
<td>80x</td>
<td>none</td>
<td>40%</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11/LKB1 mutations</td>
<td>132x</td>
<td>gastrointestinal breast</td>
<td>60%</td>
</tr>
<tr>
<td>Young age onset PC</td>
<td>FANC-C and FANC-G mutations</td>
<td>unknown</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>Family X</td>
<td>Palladin 4q</td>
<td>unknown</td>
<td>–</td>
<td>unknown</td>
</tr>
</tbody>
</table>
did not correlate with survival in a multivariate analysis. Iacobuzio-Danahue et al. [40] have shown that patients with cancer with SMAD4 (DPC4) loss usually die with diffuse metastatic disease, whereas patients with cancer with normal SMAD4 (DPC4) gene are more likely to die of localized disease. So immunolabeling for SMAD4 (DPC4) protein may be used to separate two molecular subtypes of PC, and to suggest a pancreatobiliary origin of metastatic cancer, because only few gastrointestinal carcinomas show loss of SMAD4 (DPC4) protein [1].

Jones et al. [41] reported the sequencing of 23,219 transcripts in a series of 24 PCs; the genetic changes appeared to target a core set of 12 cellular signalling pathways that were altered in 65% to 100% of the cancers. The targeted signalling pathways included: apoptosis, DNA damage control, regulation of G1/s phase transition, hedgehog signalling, homophilic cell adhesion, integrin signalling, KRAS signalling, JNK signalling, regulation of invasion, small GTPase-dependent signalling, transforming growth factor β (TGF-β) signalling, and wnt/notch signalling. These data should be useful for a molecular classification of pancreatic cancer and target therapy in the next future.

Clinical application of genetic alterations in pancreatic cancer [1]. Inherited genetic alterations can be used to quantify a person’s PC risk and patients at high risk could benefit from a close follow up to detect early PC and even the non-invasive precursors. All DACs are morphologically identical even when harboring different molecular profiles, so only an understanding of the genetic profile of PC can have direct clinical applications in evaluating the possibility of tailored therapies in the near future. In fact, gene-specific therapies that target a mutation present in a particular patient’s cancer are emerging. For example, mitomycin C and poly (ADP-ribose) polymerase (PARP) inhibitors may be particularly effective in treating PCs with BRCA2 gene mutations (that is morphologically identical to usual DACs without BRCA2 gene mutations), and it has been suggested that L-alanosine and other inhibitors of the salvage pathway of AMP synthesis may be particularly effective in treating pancreatic cancers harboring homozygous p16/CDKN2A deletions that include the MTAP gene. Medullary cancers of the pancreas often show microsatellite instability (MSI), and based on findings in colon cancer and preliminary data in pancreatic cancer; it is likely that 5-fluorouracil (5-FU) therapy will not benefit patients with MSI pancreatic cancers [1].

5. Checklist

A. Check of clinical information and completeness of clinical data

B. Macroscopic examination

1. Submitted specimen
   (a) partial or total pancreaticoduodenectomy;
   (b) distal resection;
   (c) other.

2. Tumor
   (a) location with reference to the main pancreatic duct and papilla of Vater;
   (b) size (measured in cm);
   (c) tumor appearance:
      – solid (diffuse, nodular, lobulated, hemorrhagic, necrotic)
      – cystic (unilocular, multilocular, with intraductal lesions); cyst contents (thick or thin mucoid, serous, bloody); cystic communication with pancreatic ductal tree;
      – stroma component (sclerosing, nonsclerosing);
      – tumor margins: expansive – infiltrative;
      – tumor color and consistency (tan, white, brown, red, yellow, variegated; soft, flesh, firm, scirrhous, friable, spongy);
   (d) invasion of adjacent tissue/organs;
   (e) invasion of large vessels.

3. Lesions of the noncancerous tissue
   – duct lesions (obstructions, calcifications, cysts);
   – parenchymal lesions (fibrosis, etc);
   – duodenal wall lesions.

5. Vessel segments (attached)
   Infiltrated/not infiltrated.

6. Resection margins
   Evaluation and documentation of distance and relationship between the tumor and following margins:
   (a) common bile duct margin;
   (b) pancreatic parenchyma with main duct margin;
   (c) duodenal wall (proximal and distal) margins;
   (d) circumferential resection margins:
      – anterior;
      – posterior;
      – medial (mesenteric groove).

7. Regional lymph nodes
   Regional lymph nodes subdivided following TNM rules in:
   – superior;
   – inferior;
   – anterior;
   – posterior;
   – splenic;
   – coeliac.

C. Microscopic examination

I. Tumor

   1. Histological type
   2. Histological grade
   3. Extent of invasion
      1. adjacent tissue/organs (see also macroscopy)
      2. blood vessels
      3. lymphatic vessels
      4. perineural invasion

II. Node involvement
   Number per group (total/positive) and extent of involvement of perinodal tissue

III. Resection margins
Extent/type of invasion (lymphatic and/or blood vessel invasion, dissemination of tumor cells)

IV. Noncancerous pancreas: pancreatitis, metaplasia, dysplasia

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Conflict of interest

The authors have no conflict of interest to declare.

References


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