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Adenocarcinoma of the pancreas

Ralph H. Hruban, MD^{a,b,*} and David S. Klimstra, MD^c

^aDepartment of Pathology, the Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins University School of Medicine, Weinberg 2242, 401 N Broadway, Baltimore, Maryland 21231

^bDepartment of Oncology, the Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins University School of Medicine, Baltimore, Maryland ^cDepartment of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York

Abstract

Infiltrating ductal adenocarcinoma of the pancreas is a real enigma. On one hand, it is one of the most deadly of all of the solid malignancies. On the other hand, the neoplastic glands can be remarkably well-differentiated, and it can be difficult to distinguish between a reactive non-neoplastic gland and a gland of invasive adenocarcinoma. In this review, we will present diagnostic criteria that one can “hang your hat on” when establishing the diagnosis of infiltrating ductal adenocarcinoma of the pancreas. We will also review clinically important features of the disease, and, with the impending incorporation of molecular genetics into everyday practice, we will emphasize clinical applications of cancer genetics.

Keywords

Pancreatic cancer; Pancreas cancer; Adenocarcinoma; Pancreas

Introduction

Pancreatic cancer was described in the 1760s by Giovanni Battista Morgagni in his classic book *De Sedibus et Causis Morborum per Anatomen Indigatis*.¹ Pathologists greatly refined our understanding of the gross and microscopic features of this disease in the ensuing 200 years, and gross and microscopic examination has remained the mainstay of diagnosis for centuries. The introduction of immunohistochemical labeling in clinical practice in the late 1970s and early 1980s fundamentally changed our approach to diagnoses. Soon an integration of gross and microscopic findings and immunolabeling characteristics was the norm in diagnosis. This status quo is about to be disrupted by the revolution in genetic sequencing.^{2–5}

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*Corresponding author at: Department of Pathology, the Sol Goldman Pancreatic Cancer Research Center, the Johns Hopkins University School of Medicine, Weinberg 2242, 401 N Broadway, Baltimore, MD 21231. rhruban@jhmi.edu..

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In this review, we do not throw out the clinically tested and well-established standard gross, microscopic and immunolabeling approaches to diagnosing ductal adenocarcinoma, instead we look forward to an integration of genetics as a fourth arm in our diagnostic tool box.

Gross features

Ductal adenocarcinomas are usually not subtle lesions grossly. They tend to be large (the mean size of surgically resected adenocarcinomas is 3 cm), firm, white infiltrative masses (Fig. 1).⁶ The margins of the tumor are usually ill defined, and projections of tumor can be seen extending well beyond the main mass. Larger neoplasms can have central necrosis and secondary cystic change. These cancers typically invade and obstruct associated duct systems. As a result, cancers in the head of the gland often narrow both the pancreatic duct and the distal common bile duct, producing upstream dilatation of both ducts, a finding referred to radiographically as the “double duct sign.” Cancers in the tail of the pancreas are far from the bile duct and will only obstruct the pancreatic duct. As expected, cancers in the tail of the gland are therefore often associated with a normal caliber bile duct and upstream dilatation of the pancreatic duct (Fig. 2). When these obstructive changes in the pancreatic duct system are significant, they can mimic an associated cystic or intraductal neoplasm.

The gross and microscopic changes of chronic pancreatitis are commonly associated with ductal adenocarcinomas, and sometimes the fibrosis of pancreatitis can mimic the sclerotic appearance of the carcinoma, obscuring the gross distinction between regions of carcinoma and pancreatitis. Some localized forms of pancreatitis also can simulate a carcinoma due to the appearance of a fibrotic mass involving only a portion of the organ.

Light microscopy

Infiltrating ductal adenocarcinomas are defined, as the name suggests, by the presence of invasive neoplastic glands. Two features stand out about this cancer type at the light microscopic level. First, ductal adenocarcinomas elicit an intense desmoplastic reaction, especially within the pancreas itself (desmoplasia may be less pronounced or absent in metastatic foci). This desmoplastic response can outstrip the neoplastic glands such that neoplastic cells are actually outnumbered by non-neoplastic cells in many of these tumors. The desmoplastic reaction is composed of a mixture of dense collagen, fibroblasts, delicate vessels, and inflammatory cells. The second feature that stands out about infiltrating ductal adenocarcinomas of the pancreas is that, despite the highly lethal nature of this cancer, the neoplastic glands are often extremely well-differentiated. In fact, at the light microscopic level, it can be very difficult to distinguish between the neoplastic glands of infiltrating carcinoma and the reactive glands of chronic pancreatitis. Because of this, well-defined histologic criteria need to be carefully and systematically applied when interpreting biopsies and evaluating resections.

As listed in Table 1, eight histologic features are particularly useful in the differential diagnosis of infiltrating ductal adenocarcinoma and reactive glands: (1) haphazard arrangement of the glands, (2) perineural invasion, (3) vascular invasion, (4) a gland immediately adjacent to a muscular artery, (5) luminal necrosis, (6) incomplete lumina, (7)

variation in the size of nuclei in a gland by more than four to one, and (8) “naked” glands in fat.⁶ Let us go over each of these in greater detail, since they are so very important.

The normal pancreas is composed of orderly back-to-back lobules. Small ducts are normally present at the center of these lobules and the lobules themselves are composed predominantly of acinar cells. This structure is analogous to grapes (the lobules of acinar cells) on a vine (the duct system). Chronic pancreatitis is associated with fibrosis and acinar drop-out. Even though there is loss of acinar tissue in chronic pancreatitis, the orderly rounded architecture is maintained. Extending the analogy, chronic pancreatitis can be thought of as dried grapes on a vine or, in its extreme form, a vine stripped of grapes. By contrast, infiltrating ductal adenocarcinoma is characterized by a haphazard arrangement of the glands (Fig. 3A). As the glands infiltrate the connective tissue, they no longer are restrained by an orderly architecture. Instead, some glands are oriented in one direction, other glands in another. The order of the vine structure is completely lost.

Perineural invasion is very common in ductal adenocarcinoma of the pancreas, and it indicates that the epithelial cells have the ability to invade through connective tissues and across the perineurium. Not surprisingly, perineural invasion is a useful feature in diagnosing an invasive adenocarcinoma (Fig. 3B).⁷ Perineural invasion is often best appreciated at the leading edge of the tumor, although it can be seen anywhere within the lesion. Although glands in a nerve support the diagnosis of cancer, neuroendocrine cells in a nerve do not. Instead, non-neoplastic neuroendocrine cells involving a nerve can be seen in chronic pancreatitis. Extremely rare benign glands in nerves have been reported.⁸

Vascular invasion also is common in ductal adenocarcinoma of the pancreas, and it indicates that the epithelial cells have the ability to invade through connective tissue and across the layers of the vascular walls. Like perineural invasion, vascular invasion is very common in ductal adenocarcinomas of the pancreas. One form that deserves special note is invasion of venules. For reasons that are not at all clear, when ductal adenocarcinoma invades small veins, the neoplastic cells often “re-endothelialize” the vessels. That is to say that the neoplastic cells appear to replace the endothelial cells, leaving the lumen at the center of the vessel patent (Fig. 3C). When the neoplastic cells in vessels are well-differentiated, and they often are, this structure can be very difficult to distinguish from non-invasive precursor lesions in the pancreas called “pancreatic intraepithelial neoplasia.”⁹ A well-defined layer of surrounding smooth muscle cells can help discriminate between these two entities. The walls of veins have well-oriented bundles of smooth muscle cells, and when present, these smooth muscle cells can be used to determine if a gland is in a vessel or not.

In the normal pancreas, the muscular vessels are present at the periphery of the lobules, separated from the normal ducts by numerous acinar cells. The acinar cells may be lost in chronic pancreatitis, but in most instances, the separation of ducts and muscular vessels is maintained. By contrast, because ductal adenocarcinomas invade the tissues in a haphazard manner, the neoplastic glands violate the orderly architecture and can be found immediately adjacent to muscular arteries (Fig. 3D).¹⁰ As is true for all of the features that help distinguish ductal adenocarcinoma from reactive glands, the finding of a gland immediately

adjacent to a muscular vessel is not by itself diagnostic of ductal adenocarcinoma, as it can rarely be seen in chronic pancreatitis.¹¹

The findings of luminal necrosis and incomplete lumina also support the diagnosis of invasive ductal adenocarcinoma over reactive glands (Fig. 4A).^{12,13} Luminal necrosis is defined by the presence of necrotic neoplastic cells in the glandular lumina. Luminal inflammatory cells do not count as necrotic cells. Incomplete lumina are defined by the presence of glands in which the lumina of the glands touch the stroma without intervening neoplastic epithelial cells. This feature is likely a combination of loss of cellular cohesion and increased cell turnover in invasive carcinoma.

The now famous “four-to-one rule” also helps support the diagnosis of ductal adenocarcinoma.^{14,15} The nuclei in a single reactive gland usually do not vary in size by more than four to one. That is to say, that the area of a nucleus in a benign gland will not be four times larger than its neighbor.^{14,15} The finding of nuclear size variation of greater than four to one is therefore very abnormal and suggests that the degree of pleomorphism present is more consistent with an invasive carcinoma (Fig. 4B).

Other features that support the diagnosis of invasive ductal adenocarcinoma over reactive glands include a “naked gland” touching fat, huge irregular nucleoli, and numerous, particularly abnormal, mitoses.

Importantly, knowledge of the clinical information can help prevent diagnostic mishaps. Ideally, all biopsies and intra-operative frozen-section consultations should be interpreted in light of the clinical findings.

Immunolabeling

Immunolabeling can be a useful supplement to hematoxylin-and-eosin-based diagnoses. The most common immunolabeling characteristics of ductal adenocarcinoma are provided in Table 2. Briefly, most ductal adenocarcinomas express cytokeratins (cytokeratins 7, 8, 18, 19, and variably 20), mucin (MUC1, MUC4, and MUC5AC), general cancer markers (carcinoembryonic antigen, B72.3, CA125, and carcinoma antigen 19-9), and some pancreatic cancer-specific markers (mesothelin, S-100A4, etc.). In addition, immunolabeling for antigens that function as surrogate markers for genetic changes can also be altered in ductal adenocarcinomas. Most ductal adenocarcinomas have abnormal nuclear labeling with antibodies to TP53, and 55% show a loss of Smad4 expression (Fig. 5).^{16–18}

The immunolabeling characteristics of the desmoplastic stroma have also been characterized.^{19–21} As will be discussed later in this review, some of the genes expressed in the desmoplastic stroma are attractive targets for novel therapies.^{19,22}

Genetic sequencing

As emphasized in all of the reviews in this issue of *Seminars in Diagnostic Pathology*, the exomes (all known coding genes) of all of the major tumor types of the pancreas have been sequenced and tumors of the pancreas are among the best characterized neoplasms at the

genetic level.^{2–5,23,24} The genes targeted in ductal adenocarcinomas of the pancreas are listed in Table 3. Briefly, there are four genetic “mountains” in ductal adenocarcinomas (genes that are targeted in >50% of the cancers). These include an oncogene, *KRAS*, and three tumor-suppressor genes, *TP53*, *p16/CDKN2A*, and *SMAD4*. In addition to these genetic mountains, there are a number of “hills,” genes that are targeted in a minority of pancreatic cancers. These include *ARID1A*, *ATM*, *AKT2*, *MAP2K4*, *MLL3*, *TGFβR2*, and *FBXW7*.^{2,5,24} In addition to these somatic (acquired) mutations, a number of germline (inherited) genetic alterations have been identified that predispose the person carrying the germline genetic alteration to the development of pancreatic cancer. These include germline mutations in *BRCA2*, *BRCA1*, *PALB2*, *p16/CDKN2A*, *STK11*, *ATM*, *PRSS1*, and the DNA repair genes (such as *MSH2*).^{25–27} The challenge of the next decade, as outlined below, will be to translate these genetic discoveries to improving patient care.

Applying advances to tumor classification

Recent advances in our understanding of the patterns of gene expression and of the mutations targeted in ductal adenocarcinoma are already being applied clinically to the care of patients in a number of ways.

One of the best examples of a clinical application of pancreatic cancer genetics is immunolabeling for the protein product of the *SMAD4* (also known as *DPC4*) gene.¹⁶ *SMAD4* is genetically inactivated in ~55% of invasive ductal adenocarcinomas, and *SMAD4* is only rarely targeted in other tumor types. Immunolabeling for Smad4, the protein product of the *SMAD4* gene, accurately reflects gene status.¹⁶ Therefore loss of Smad4 immunoexpression by cells in the pancreas would support a diagnosis of carcinoma rather than reactive atypia. Smad4 loss can also point to a pancreatic primary in a metastasis of unknown origin (Fig. 5A), although adenocarcinomas of other organs can also exhibit Smad4 loss less commonly. In addition, *SMAD4* gene status has prognostic significance, with loss of Smad4 being associated with a worse prognosis and more widespread metastases in patients with ductal adenocarcinomas.^{28,29}

Genetics can also be used to define subtypes of ductal adenocarcinoma, especially when genetic findings are integrated with tumor morphology and immunolabeling. For example, for decades, all undifferentiated carcinomas were all lumped together. Today it is recognized that undifferentiated “medullary” carcinomas, defined by pushing borders, a syncytial growth pattern and necrosis, are often microsatellite unstable.³⁰ Importantly, microsatellite unstable medullary carcinomas, despite their poor differentiation, carry a better prognosis than do classic ductal adenocarcinomas. In addition, medullary carcinomas may not respond well to 5-fluorouracil-based chemotherapeutic regimens, and patients with a medullary carcinoma are more likely to have a positive family history of cancer than are patients with a standard ductal adenocarcinoma of the pancreas.^{30–33} This latter observation may be explained by the increased risk of pancreatic cancer observed in individuals with hereditary non-polyposis colorectal cancer syndrome.³⁴

Another example of how molecular tools can be used to improve tumor classification is the use of immunolabeling for e-cadherin in prognostication (Fig. 6). Winter et al.³⁵ examined a

large series of patients with pancreatic cancer who underwent a curative pancreatic resection and found that e-cadherin loss in the neoplastic cells, as defined by immunolabeling, was associated with the presence of poorly cohesive cells and a very poor patient prognosis.

Applying advances to tumor treatment

While the desmoplastic stroma that characterizes ductal adenocarcinoma has been viewed as a barrier to treatment,³⁶ it has also been hypothesized that genes selectively overexpressed in the stroma could be supplanted to deliver selectively chemotherapeutic agents specifically to the tumor microenvironment. For example, SPARC (secreted protein acidic and rich in cysteine), also known as osteonectin, is overexpressed in desmoplastic stroma of pancreatic cancer, and it has been suggested that the albuminized form of taxol, called nab-paclitaxel, preferentially binds to SPARC. This suggests a mechanism to selectively deliver a chemotherapeutic agent to the tumor. von Hoff et al.²² tested this in a clinical trial and reported an improved survival in pancreatic cancer patients treated with nab-Paclitaxel combined with gemcitabine. While the jury is still out on whether the improved survival is the result of nab-paclitaxel binding SPARC, or from some other mechanism, these results do show the power of using an understanding of tumor biology to advance novel therapies.

Gene expression by the neoplastic cells themselves can also guide therapy. For example, the expression of the human equilibrative nucleoside transporter (hENT1) is a predictive marker for gemcitabine sensitivity.³⁷ A meta-analysis of gemcitabine metabolic genes in over 600 patients with pancreatic cancer found that high expression of hENT1 by the cancer cells was associated with improved overall and disease-free survival.³⁷ As noted earlier, the loss of Smad4 immunolabeling by the cells of ductal adenocarcinoma has been associated with a worse prognosis and more widespread metastases.^{28,29} This finding suggests that Smad4 status could be used to guide the choice of local vs. systemic therapy in patients with borderline resectable pancreatic cancer.

Infiltrating ductal adenocarcinomas that arise in association with an intraductal papillary mucinous neoplasm (IPMN) often harbor inactivating mutations in the *RNF43* gene.³ *RNF43* codes for a protein, rnf43, that regulates the expression of frizzled and which therefore plays a role in the β -catenin pathway, and it has been suggested that invasive ductal adenocarcinoma with inactivating mutations in *RNF43* may be selectively sensitive to agents that block the β -catenin pathway.^{3,38}

A number of inherited (germline) genetic alterations are also potentially therapeutically targetable and provide a unique opportunity for personalized medicine. Germline mutations in one of the Fanconi anemia pathway genes, including *BRCA1*, *BRCA2*, and *PALB2* (also known as *FANCN*), increase the risk of pancreatic cancer.^{25–27} Fanconi anemia pathway genes code for proteins that help repair DNA cross-linking damage. Therefore, pancreatic cancers in which one of these genes is genetically inactivated should be exquisitely sensitive to treatments that induce DNA cross-linking damage or which further impede DNA repair. Indeed, several dramatic clinical responses to mitomycin C and to inhibitors of poly (ADP-ribose) polymerase (PARP) have been reported in pancreatic cancer patients with cancers that harbor inactivating mutations in a Fanconi anemia gene.^{39,40}

Similarly, germline mutations in the *ATM* gene predispose to pancreatic cancer, and the ataxia telangiectasia-mutated (ATM) pathway is also potentially therapeutically targetable with existing agents.^{24,25} PARP inhibitors, external beam radiation therapy and DNA-PKcs (protein kinase DNA-activated catalytic polypeptide) inhibitors may all be selectively effective in these patients.^{41,42}

The take-home message of all of this is that soon pathologists will be asked not only about cancer morphology, but also about the genetic background in which the cancer has arisen. As William Osler said, “the good physician treats the disease; the great physician treats the patient who has the disease.”⁴³

Pancreatic intraepithelial neoplasia

No discussion of invasive ductal adenocarcinoma would be complete without including the precursor lesions that give rise to invasive cancer of the pancreas. These include IPMNs, mucinous cystic neoplasms (MCNs), and pancreatic intraepithelial neoplasia (PanIN). IPMNs and MCNs are discussed extensively elsewhere in this issue, here we will focus on PanINs.

PanIN lesions are defined histologically as small (usually <0.5 cm) intraductal mucin-producing, usually papillary, neoplasms that usually grow in the smaller pancreatic ducts.^{6,44,45} PanIN lesions are graded based on the degree of architectural and cellular dysplasia from PanIN-1 (low-grade) to PanIN-2 (intermediate-grade) to PanIN-3 (high-grade) (Fig. 7).^{6,44,45} PanIN-1 lesions can be further subdivided into those that are flat (PanIN-1A) and those that are papillary (PanIN-1B). Three features help distinguish PanINs from IPMNs.^{6,44,45} First, IPMNs are, by definition, larger than Pan-INs. IPMNs are usually grossly visible, and, by definition are ≥ 1 cm. Second, IPMNs tend to have long slender papillae, while PanINs have short stubby papillae. Third, many IPMNs, particularly those with an “intestinal” morphology, produce copious amounts of luminal mucin. PanINs do not. We tend to use the terminology “incipient IPMNs” for the lesions that fall between 0.5 and 1.0 cm, and that have intermediate histologic features.⁴⁶

The identification of shared genetic changes in PanIN lesions and in infiltrating ductal adenocarcinomas has helped establish that PanINs are the precursor lesions to invasive ductal adenocarcinoma.^{47,48} Mouse models also support the progression of PanIN lesions to invasive cancer, as mice genetically engineered to harbor *KRAS* gene mutations in their pancreas first develop PanIN lesions (called mPanINs in the mouse) and subsequently develop invasive ductal adenocarcinoma.⁴⁹ While PanIN lesions clearly can be precursors to invasive pancreatic cancer, the speed and frequency at which PanINs progress have not been established. In a “back-of-the-envelope” calculation, Terhune et al.⁵⁰ estimated that less than 1% of PanINs progress to invasive cancer. As is discussed below, the very low risk posed by a single PanIN lesion needs to be considered when interpreting pancreatic margins and making other clinical decisions.

Just as adenomas can be found in colons with an invasive colon cancer, so too does the pancreatic parenchyma adjacent to an invasive ductal adenocarcinoma often contains multiple PanIN lesions. While this association helps establish the relationship between

PanINs and invasive cancer, the finding of PanIN lesions at a margin can be problematic. First, these PanIN lesions can mimic an invasive cancer. Careful application of the eight “rules” listed in Table 1 can help distinguish between these two entities. Second, the clinical significance of a PanIN lesion at a margin can easily be overemphasized. Efforts to resect pancreatic parenchyma until no PanIN lesions are seen at a margin can lead to additional, often unnecessary, surgery. Matthaei and colleagues reported a large series of patients who had a ductal adenocarcinoma surgically resected with negative (R0) margins.⁵¹ PanIN lesions were present at the pancreatic parenchymal margin in half of these patients. There were no significant differences in survival between the patients with a PanIN, even of a high-grade PanIN, at the margin and those without a PanIN at the margin.⁵¹ This should not be surprising considering the highly lethal nature of most invasive pancreatic cancers and the low rate and frequency at which PanINs progress to invasive cancer. Sadly, most patients die of their invasive carcinoma before any PanIN lesions they have had the time to progress. Stated simply, if a patient has an invasive ductal adenocarcinoma of the pancreas, do not overtreat PanINs at a margin. PanINs are the least of the patient’s problems. A similar comment applies to the significance of a lower-grade PanIN lesion detected in a pancreas that lacks an invasive carcinoma. Given the low rate of progression from PanIN-1 or PanIN-2 to invasive carcinoma, the clinical significance of isolated foci of low grade PanIN is negligible, and some authorities question with such lesions should be included in pathology reports as they may lead our clinical colleagues to overtreat their patients.

As discussed earlier, infiltrating ductal adenocarcinomas often invade small vessels, and when they do, the neoplastic cells can replace the endothelial cells and mimic a PanIN lesion (Fig. 3C).⁹ In contrast to PanIN lesions, these small vessels will have well-oriented bundles of smooth muscle cells in their walls.

Summary and conclusions

It used to be that pancreas surgery was only performed at a few specialized centers. However, many of the residents and fellows trained in these programs have started their own pancreas surgery programs in a wide array of institutions. As a result, pathologists, even pathologists at smaller centers, are likely to face the challenge of having to interpret pancreas pathology.

In this review, we have tried to provide a practical approach to distinguishing between infiltrating ductal adenocarcinoma and its mimics, and we have tried to demonstrate how molecular genetics can now be integrated into the care of patients with this cancer.

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Fig. 1.
Gross feature of a fibrotic pancreatic cancer. The carcinoma surrounds a large artery.

Fig. 2.
Gross feature with upstream ductal dilatation. The normal duct is seen on the left, the tumor is present in the center, and a dilated duct upstream from the cancer is on the right.

Fig. 3. Histologic features that support the diagnosis of infiltrating ductal adenocarcinoma include (A) glands arranged haphazardly, (B) perineural invasion, (C) venous invasion, and (D) a gland immediately adjacent to a muscular artery (all hematoxylin and eosin stained).

Fig. 4. Other histologic features supporting the diagnosis of adenocarcinoma include luminal necrosis and incomplete lumina (A), and nuclear variation in a single gland of greater than four to one (B) (both hematoxylin and eosin stained).

Fig. 5. The genes most commonly targeted in pancreatic cancer include *KRAS*, *p16/CDKN2A*, *TP53*, and *SMAD4*. Loss of expression of Smad4 (A) and over-expression of tp53 (B) by immunolabeling can be used as surrogate markers for genetic alterations in these genes.

Fig. 6.

Loss of expression of e-cadherin is seen in some poorly differentiated carcinomas and is associated with a poor prognosis. Note the intact membranous expression in non-neoplastic acinar cells (right) and the loss of expression in the poorly differentiated carcinoma on the left. (Immunolabeling for e-cadherin.)

Fig. 7. Pancreatic intraepithelial neoplasia (PanIN)-2 (A) and PanIN-3 (B) (both hematoxylin and eosin stained).

Table 1

Eight features supportive of the diagnosis of ductal adenocarcinoma.⁶

Ductal adenocarcinoma	Reactive glands
Haphazard arrangement of the glands	Lobular arrangement of glands
Perineural invasion	Neuroendocrine cells can abut nerves
Vascular invasion	Not seen
Gland immediately adjacent to a muscular artery	Glands separated from muscular vessels by acinar cells or by orderly rounded connective tissue
Luminal necrosis	Can have polymorphonuclear leukocytes, but not epithelial necrosis
Incomplete lumina	Epithelial cells form a complete ring around lumina
Four-to-one rule	Nuclei in a single gland vary by less than four to one
“Naked” glands in fat	Glands in fat have associated connective tissue

Table 2

Immunolabeling characteristics of ductal adenocarcinoma⁶ and the associated desmoplastic stroma.

In the neoplastic cells	
Cytokeratins	CK7, 8, 18, 19, and $\pm$ 20
Mucins	MUC1, MUC3, MUC4, and MUC5AC
Cancer markers	CEA, CA19-9, B72.3, DUPAN-2, and CA125
Mutational markers	SMAD4 (lost) and TP53 (labeling gained)
Others	Mesothelin, PSCA, claudin 4, S-100A4, A-100A6, and S-100P
In the stromal cells	
	SPARC and fibronectin
Inflammatory cells	CD3, CD4, CD8, Tregs (FOXP-3), CD20, and MAC387

Table 3Genes mutated in ductal adenocarcinoma.^{2,5,24}

Gene	Chromosome	Percentage of cancers/ families
Somatic genetic changes		
<i>KRAS2</i>	12p	90–95
<i>p16/CDKN2A</i>	9p	90
<i>TP53</i>	17p	75
<i>SMAD4</i>	18q	55
<i>ARID1A</i>	1p	<3
<i>ATM</i>	11q	<3
<i>AKT2</i>	19q	<3
<i>MAP2K4</i>	17p	<3
<i>MLL3</i>	7q	<3
<i>TGFβR2</i>	3p	<3
<i>FBXW7</i>	4q	<3
Germline genetic changes		
<i>BRCA1</i>	17q	1–2
<i>BRCA2</i>	13q	6–12
<i>PALB2</i>	16p	3
<i>ATM</i>	11q	2
<i>STK11</i>	19p	<1
<i>PRSS1</i>	7q	<1
<i>P16/CDKN2A</i>	9p	1–3
Mismatch repair	Multiple	?