Precursors to Invasive Pancreatic Cancer

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Abstract: Pancreatic cancer, once invasive, is almost uniformly fatal. In order to alleviate the dismal prognosis associated with this disease, it is imperative that pancreatic cancer be recognized and treated prior to invasion. Understanding the morphology and biology of precursor lesions of invasive pancreatic cancer has therefore become an issue of paramount importance. In the last decade, significant progress has been in the recognition and appropriate classification of these precursor lesions, and the current review will focus on our state-of-the-art knowledge on this topic. Mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), and pancreatic intraepithelial neoplasia (PanIN) encompass the three known morphologically distinct precursors to invasive pancreatic cancer. In addition to discussion of the “classic” precursor entities, this review will also address some of the recent diagnostic controversies for these lesions, in particular features that distinguish IPMNs from PanIN lesions. Finally, the potential clinical impact of recognizing these precursor lesions in the context of early detection of pancreatic cancer will be discussed.

Key Words: pancreatic cancer, intraductal papillary mucinous neoplasm, pancreatic intraepithelial neoplasia, mucinous cystic neoplasm

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In the year 2005, it is estimated that worldwide 213,000 people will be diagnosed with pancreatic cancer and 213,000 will die of it. The figures are equally dismal in the United States, where this year 31,000 Americans will be diagnosed with pancreatic cancer and 31,000 will die of the disease. It is particularly disturbing that despite enormous progress made in our understanding of the genetics of invasive pancreatic cancer, the survival figures for pancreatic cancer have not changed significantly in the last four decades (Fig. 1) (http://www.kreftregisteret.no).

Significant progress has been made, however, in understanding the precursor lesions that give rise to invasive pancreatic cancer, and these precursors offer exciting new targets for chemoprevention and early detection efforts. Here we review three well-defined precursors to invasive cancer: mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), and pancreatic intraepithelial neoplasia (PanIN).

MUCINOUS CYSTIC NEOPLASMS

MCNs are distinctive mucin-producing epithelial neoplasms with a characteristic ovarian-type stroma. Most (90%) of MCNs occur in females, and the average age at diagnosis is approximately 50 years. In most series, patients with non-invasive MCNs are significantly younger than patients with invasive MCNs. For example, Leborgne et al found a mean age of 50 years for patients with MCN adenoma as compared with 65 years for patients with invasive MCN (P < 0.001). Most patients present with vague abdominal symptoms such as abdominal pain, anorexia, or a sense of fullness, whereas other patients are asymptomatic and are diagnosed on a physical examination or abdominal imaging for another indication. Computed tomography (CT) will typically reveal a large (mean 10-cm) well-defined cystic mass in the tail of the pancreas. The cysts are usually fairly large (1–3 cm), separated by fibrous septa; the contents of the cysts within an MCN vary in attenuation, as some contain mucin and others more hemorrhagic fluid. In most cases, endoscopic retrograde cholangiopancreatography will reveal that the cysts do not communicate with the pancreatic duct, when there is a communication it is tenuous, and, in contrast to IPMNs, intraductal growth is not seen.

Grossly, MCNs typically form large multilocular cystic masses in the tail of the pancreas. The average size of an MCN is about 10 cm, the external surface is usually smooth, and cut section reveals multiple well-defined cysts separated by fibrous septa. Some of the cysts contain thick tenacious mucin, whereas others will contain slightly more watery hemorrhagic material. Importantly, these cysts usually do not communicate with the pancreatic ducts; as noted above, in the rare cases in which a communication can be demonstrated, intraductal spread of the neoplasm is not seen.

Two distinct components are seen at the light microscopic level (Fig. 2). The epithelial component consists of columnar mucin-producing cells with varying degrees of architectural and nuclear atypia. The epithelium can be flat or papillary, and epithelium with significant dysplasia is often immediately adjacent to entirely benign epithelium (Fig. 3).

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An invasive component is present in one-third of MCNs, and this invasive component can be quite focal.\textsuperscript{6,7,9,13,17} Thorough, if not complete, sampling for histologic examination is therefore needed to rule out the presence of a small invasive cancer.

A distinct “ovarian-type” of stroma forms the second component of these neoplasms (see Fig. 2).\textsuperscript{7,14} This ovarian-type stroma typically forms a band of densely packed spindle-shaped cells immediately beneath the neoplastic epithelium. These spindle-shaped cells can even show luteinization. It should be noted that the epithelium is frequently focally denuded, and in these cases, the ovarian-type stroma can be a very useful diagnostic feature at the time of frozen-section diagnosis.

Immunohistochemical labeling will demonstrate the expression of keratins (AE1/AE3, CAM5.2), epithelial membrane antigen, carcinoembryonic antigen (CEA), and mucin (MUC5AC) by the epithelial cells and the expression of smooth muscle actin, progesterone receptors (60–90%), \(\alpha\)-inhibin (90%), and estrogen receptors (30%) by the stromal cells.\textsuperscript{11,18–22} Labeling for endocrine markers such as chromogranin often reveals scattered intraepithelial endocrine cells.\textsuperscript{6,11,14,19} Recent global analysis of gene expression in MCNs has revealed the overexpression of S100P, prostate stem cell antigen, jagged 1, c-myc, cathepsin E, and pepsinogen C by the neoplastic epithelium and the overexpression of several genes involved in estrogen metabolism, including steroidogenic acute regulatory protein (\textit{STAR}) and estrogen receptor-1 (\textit{ESR1}), by the ovarian-type stroma.\textsuperscript{23}

It should be noted that ovarian-type stroma is required in the current definition of MCNs. Many neoplasms previously classified as MCN lacked an ovarian-type stroma and would now be classified as an IPMN. Because of the more stringent requirement for ovarian-type stroma, the proportion of MCNs relative to IPMNs is declining in most series.
At the DNA level, activating point mutations in the KRAS2 oncogene occur early, whereas inactivation of TP53 and DPC4/MADH4 has been reported in invasive MCNs.\textsuperscript{14,19,24–28} As noted earlier, an invasive tubular/ductal adenocarcinoma is present in about one-third of all surgically resected MCNs. If the neoplasm is surgically resected and an invasive carcinoma is not identified after thorough histologic examination of the neoplasm, then the patient will have an excellent prognosis. In most series, patients with entirely resected and histologically completely examined noninvasive MCNs are cured.\textsuperscript{9,10,13,14,29,30} By contrast, patients with an invasive carcinoma have a 60% 5-year survival rate.\textsuperscript{9,10,29,30} In addition, several studies have shown that the size of the invasive component in MCNs has prognostic significance.\textsuperscript{14} Therefore, it is essential that the size of the invasive and the size of the noninvasive components of an MCN be reported separately. For example, a pathology report could read as follows: "2 cm moderately differentiated ductal adenocarcinoma arising in association with a 10-cm mucinous cystic neoplasm with carcinoma in situ."

The dramatic difference in prognosis for patients with noninvasive and invasive MCNs highlights the enormous importance of diagnosing and surgically resecting noninvasive MCNs before they progress to an invasive carcinoma. Some patients with MCNs have symptoms for years before they are diagnosed, suggesting that the "window of opportunity" for detecting and treating noninvasive MCNs is significant.

**INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS**

IPMNs are mucin-producing epithelial neoplasms that, by definition, involve the main and/or branch pancreatic ducts.\textsuperscript{4,5,31,32} IPMNs occur in men slightly more frequently than they do in women (male/female ratio of 60:40), and the average age at diagnosis is 60–65 years.\textsuperscript{8,33–39} In one series, the average age at diagnosis for patients with a noninvasive IPMN adenoma was 63 years, whereas for patients with an invasive IPMN, it was 68 years.\textsuperscript{33,40} Presenting signs and symptoms include abdominal pain, weight loss, steatorrhea, and pancreatitis.

Abdominal imaging, including CT, will reveal a cystic lesion, usually in the head of the pancreas.\textsuperscript{41} In contrast to MCNs, the cystic lesions of an IPMN typically communicate with and extensively involve the large pancreatic ducts. The endoscopic demonstration of mucin oozing from a patulous ampulla of Vater is an almost diagnostic feature of an IPMN.\textsuperscript{42,43}

Grossly, the majority of IPMNs arise in the head of the pancreas (75%); however, IPMNs can also arise in the body or tail of the gland (20%), and some IPMNs diffusely involve the entire length of the pancreas.\textsuperscript{35,39,42,44} By definition, IPMNs involve either the main pancreatic duct or its branches or both. A very helpful procedure in the gross examination of a surgically resected IPMN is to place a probe in the main pancreatic duct. The specimen can then be bivalved along the probe and the relationship between the main duct and papillary growths or cystic lesions clearly demonstrated. IPMNs produce copious amounts of mucin, and this mucin typically diffusely or focally dilates the pancreatic ducts. Serial sections of the entire pancreatic specimen and three-dimensional reconstruction are extremely useful in determining the full extent of IPMNs.

Two features characterize IPMNs at the light microscopic level. First, as noted above, the neoplastic epithelium, by definition, involves main and/or branch pancreatic ducts, which may be dilated (Fig. 4). Second, the neoplastic epithelium is mucin producing and typically papillary (Fig. 5). As was true for MCNs, the degree of architectural and nuclear atypia within an IPMN can be dramatically heterogeneous, and invasive cancers can be focal. Extensive histologic sampling is therefore needed to assess for the presence or absence of an associated invasive carcinoma. Microscopically, multifocal IPMNs have been reported.\textsuperscript{45–49}

**FIGURE 4.** IPMN. By definition, these neoplasms involve the larger pancreatic ducts.

**FIGURE 5.** Intestinal-type IPMN. Note the papillae, the abundant mucin production, and the absence of "ovarian-type" stroma.
Recent global analyses of gene expression have demonstrated the expression of cytokeratin (CK7), CEA, MUC5AC, and CA19.9. As will be discussed later in the section on subtyping IPMNs, those IPMNs with intestinal differentiation usually express MUC2 and CDX2, but not MUC1, whereas those IPMNs with pancreatobiliary differentiation usually express MUC1, but not MUC2 or CDX2. IPMNs with gastric foveolar differentiation are MUC5AC positive but usually do not express either MUC1 or MUC2.

TABLE 1. Features Useful in Distinguishing Between IPMNs and MCNs

| Feature                        | MCN     | IPMN    |
|--------------------------------|---------|---------|
| Age at diagnosis (y)           | 55      | 65      |
| Gender                         | 90% F   | 40% F   |
| Location in pancreas           | Tail    | Head    |
| Growth within larger pancreatic ducts | No      | Yes     |
| Mucin oozing from ampulla      | No      | Yes     |
| Ovarian-type stroma            | Yes     | No      |
| Extrapancreatic neoplasms      | No      | Yes     |
Criteria useful in distinguishing between IPMNs and MCNs are provided in Table 1.

RECENT CONTROVERSIES IN INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Two controversies have recently emerged in the classification of IPMNs. First, it has been noted that some IPMNs arise in branches of the main pancreatic duct.93-98 These “branch duct” IPMNs, first described by Kuroda in 1988,93 often show gastric differentiation and are often histologically low-grade lesions (adenomas), suggesting that they may be biologically and clinically distinct from the larger main duct-type IPMNs with intestinal differentiation (Table 2).95,98,99 For example, Terris et al examined 43 IPMNs and classified 13 (30%) of these as branch duct type and 30 (70%) as main duct type.98 The mean age of the patients with branch duct type IPMNs was 64 years compared with 55 years for those with main duct type IPMNs. The branch duct type IPMNs tended to be smaller, 12 of the 13 branch duct type IPMNs were confined to the head of the gland (particularly the uncinate), and 85% showed minimal atypia. Only 15% harbored a carcinoma in situ, and none was associated with an invasive carcinoma. By contrast, 17 of the 30 main duct type IPMNs involved the head of the gland, and only 43% showed minimal atypia. Twenty percent of the main duct-type IPMNs were carcinoma in situ and 37% had an associated invasive carcinoma.98 The reported proportions of branch duct and main duct IPMNs are not the same in all studies.8 For example, of the 28 IPMNs reported by Fukushima et al, 11 were branch duct type, 5 main duct type, and 11 combined.8 Three of the 5 main duct type IPMNs were associated with an invasive carcinoma, as were 3 of the 11 branch duct type IPMNs.8 The wide disparity in the reported proportion of branch duct to main duct types of IPMNs suggests that the diagnostic criteria for distinguishing between these two variants of IPMNs need to be better defined.

With the growing recognition of small asymptomatic IPMNs, the clinical distinction between main duct and branch duct type IPMNs will only increase in importance. Whether branch duct and main duct type IPMNs represent ends of a spectrum or distinct entities has yet to be resolved.

The second recent controversy in the study of IPMNs is the histologic classification of the types of epithelium seen. The first IPMNs described were predominately large mucin-producing papillary neoplasms with “intestinal” differentiation (see Fig. 5). The neoplastic epithelial cells of IPMNs with intestinal differentiation are columnar cells with cigar-shaped nuclei, and they express MUC2, MUC5AC, and CDX2, but not MUC1.56,62 More recently, however, it has been recognized that neoplasms that meet the definition of an IPMN can show a much broader spectrum of differentiation.46,56,62,100 Some, such as most branch duct type IPMNs, show mostly a “gastric foveolar” type of differentiation (Fig. 7) and express MUC5AC, but neither MUC1 nor MUC2, whereas others are more poorly differentiated with complex branching papillae and micropapillae and express MUC1 and MUC5AC, but not MUC2. These latter IPMNs are usually at least carcinoma in situ and are often referred to as “pancreatobiliary”-type IPMNs (Fig. 8). These morphologic distinctions appear to be clinically important because they often progress to different types of invasive cancer. Most intestinal-type IPMNs are believed to progress to invasive colloid carcinomas, which also express MUC2 and have a good prognosis, whereas most pancreatobiliary IPMNs are believed to progress to invasive cancers.

| TABLE 2. Features Useful in Distinguishing Between Main and Branch Duct IPMNs98,123 |
|-------------------|-------------------|
| **Main** | **Branch** |
| Age (y) | 55 | 65 |
| Location in pancreas (% head) | 57 | 93 |
| Dysplasia (%) | | |
| Adenoma | 43 | 85 |
| Carcinoma in situ | 20 | 15 |
| Invasive | 37 | 0 |

FIGURE 7. IPMN with gastric foveolar differentiation.

FIGURE 8. IPMN with pancreatobiliary differentiation.
ductal/tubular adenocarcinomas, which express MUC1, but not MUC2, and have a poor prognosis.66,62 Gastric-type epithelium is often found at the periphery of other types of IPMNs, and it is also true that some IPMNs contain both “intestinal” and “pancreatobiliary” foci. It is currently unclear whether histologically gastric-type IPMNs progress to intestinal-type and intestinal-type progresses to pancreatobiliary IPMNs.

MARGINS IN PATIENTS WITH INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Patients with surgically resected noninvasive IPMNs have an excellent prognosis, yet the neoplastic epithelium in an IPMN can extend intraductally for several centimeters beyond the grossly dilated duct.101 Careful intraoperative frozen section evaluation of pancreatic margins is therefore, in our opinion, critical to the surgical management of patients with an IPMN. The extension of an IPMN to a surgical margin and the degree of atypia at the sectioned margin should be communicated to the surgeon so that the surgeon can integrate this information with the patient’s wishes and the patient’s clinical status to determine if the resection of additional pancreatic parenchyma is warranted.

The importance of finding a dilated duct completely denuded of its epithelium or PanIN (see below) at a surgical margin is less clear. In our experience, the neoplastic epithelium in an IPMN is often denuded in areas with intense inflammation. We therefore believe that, at a minimum, additional sections deeper into the block should be taken when there is complete epithelial denudation in a larger duct. By contrast, in our experience, low-grade PanINs are so common in pancreata with an IPMN that nothing more should be done if low-grade PanINs are found at the margin. When high-grade dysplasia is present in a small duct at a margin, the finding should be carefully evaluated to determine whether it is a separate PanIN-3 or extension of carcinoma in situ of the IPMN. It must be noted that the invasive carcinoma along preexisting pancreatic ducts (“cancerization of the duct”) may mimic PanIN-3. The finding of PanIN-3 at a margin should be discussed with the surgeon and integrated into preoperative findings from imaging studies and the operative gross findings. Clearly, the finding of invasive cancer at a margin warrants the resection of additional pancreatic tissue if the patient can tolerate it.

PANCREATIC INTRAEPITHELIAL NEOPLASIA

Noninvasive epithelial lesions have been recognized in the smaller pancreatic ducts for close to 100 years.102 A large number of terms have been used to designate these lesions, but in 2001, an international consensus established the “pancreatic intraepithelial neoplasia” (PanIN) nomenclature.103 PanINs were defined as neoplastic epithelial proliferations in the smaller-caliber pancreatic ducts, and PanINs were divided into three grades based on the degree of architectural and nuclear atypia present (Fig. 9). The diagnostic criteria for each grade of PanIN are given in Table 3, and numerous examples are available on the John Hopkins web site (http://pathology2.jhu.edu/pancreas_panin).103 In contrast to IPMNs, most PanINs express MUC1, MUC5AC, and MUC6.104 MUC6 is a pyloric gland mucin and MUC5AC a gastric foveolar mucin, and their
TABLE 3. Existing PanIN Nomenclature

| Normal: The normal ductal and ductular epithelium is a cuboidal to low-columnar epithelium with amphiphilic cytoplasm. Mucinous cytoplasm, nuclear crowding, and atypia are not seen. Squamous (transitional) metaplasia: A process in which the normal cuboidal ductal epithelium is replaced by mature stratified squamous or pseudostratified transitional epithelium without atypia. | Invasive Adenocarcinoma
|---|---|
| Pancreatic intraepithelial neoplasia-1A (PanIN-1A): These are flat epithelial lesions composed of tall columnar cells with basally located nuclei and abundant supranuclear mucin. The nuclei are small and round to oval in shape. When oval, the nuclei are oriented perpendicular to the basement membrane. It is recognized that there may be considerable overlap between nonneoplastic flat hyperplastic lesions and flat neoplastic lesions without atypia. Therefore, some may choose to designate these entities with the modifier term “lesion” (“PanIN/L-1A”) to acknowledge that the neoplastic nature of many cases of PanIN-1A has not been unambiguously established. Pancreatic intraepithelial neoplasia-1B (PanIN-1B): These epithelial lesions have a papillary, micropapillary, or basally pseudostratified architecture but are otherwise identical to PanIN-1A. Pancreatic intraepithelial neoplasia-2 (PanIN-2): Architecturally, these mucinous epithelial lesions may be flat but are mostly papillary. Cytologically, by definition, these lesions must have some nuclear abnormalities. These abnormalities may include some loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromatism. These nuclear abnormalities fall short of those seen in PanIN-3. Mitoses are rare but, when present, are nonluminal (not apical) and are not atypical. True cribriform structures with luminal necrosis and marked cytologic abnormalities are generally not seen and, when present, should suggest the diagnosis of PanIN-3. Pancreatic intraepithelial neoplasia-3 (PanIN-3): Architecturally, these lesions are usually papillary or micropapillary; however, they may rarely be flat. True cribriforming, the appearance of “budding off” of small clusters of epithelial cells into the lumen, and luminal necrosis should all suggest the diagnosis of PanIN-3. Cytologically, these lesions are characterized by a loss of nuclear polarity, dystrophic goblet cells (goblet cells with nuclei oriented toward the lumen and mucinous cytoplasm oriented toward the basement membrane), mitoses that may occasionally be abnormal, nuclear irregularities, and prominent (macro)nucleoli. The lesions resemble carcinoma at the cytological level, but invasion through the basement membrane is absent. | Invasive ductal adenocarcinoma is a histologically invasive malignancy that extends beyond the confines of the ductal epithelium. The tumor is characterized by infiltrative growth into surrounding tissues, destruction of normal tissue architecture, and invasion through the basement membrane. The neoplastic cells show loss of differentiation, increased mitotic activity, and anaplasia. The development of a two-tier grading system will be needed. Such a two-tier system could combine PanIN-1 and PanIN-2 under the designation “low-grade PanIN” and leave PanIN-3 as “high-grade PanIN.” The establishment of the PanIN nomenclature has proven invaluable in developing a genetic progression model for small noninvasive duct lesions in the pancreas. It is now clear that just as there is a progression in the colorectum from adenoma to adenoma with dysplasia to invasive cancer, so too is there a histologic and genetic progression from PanIN-1 to PanIN-2 to PanIN-3 to invasive ductal adenocarcinoma in the pancreas. Early genetic alterations include telomere shortening and KRA S2 activation, intermediate alterations and the inactivation of the p16/CDKN2A tumor suppressor gene, and late alterations and the inactivation of the TP53 and DPC4/SMAD4 tumor suppressor genes. In addition, specific patterns of gene expression in the various grades of PanIN have emerged, providing an array of new markers for early pancreatic cancer and new targets for chemoprevention. For example, we have shown that cyclo-oxygenase-2 is expressed in 36% of PanINs. The development of the PanIN classification system has also helped in the interpretation of mouse models of pancreatic cancer and its precursors. PanINs are also important because they can morphologically mimic invasive ductal adenocarcinoma. A number of diagnostic features are helpful in distinguishing PanINs from invasive cancer (Table 4). In contrast to reactive ducts and PanINs, invasive ductal adenocarcinomas demonstrate (a) incomplete lumina, (b) a variation in nuclear size of >4:1 in a single duct, (c) luminal necrosis, (d) perineural invasion, (e) vascular invasion, (f) glands next to muscular vessels, and, most importantly, (g) a haphazard growth pattern. Two controversies have recently emerged in the study of PanINs. First, three grades were established in the original PanIN nomenclature (PanIN-1, PanIN-2, and PanIN-3). Although this three-tier grading system has proven extremely useful to researchers comparing molecular analyses performed at different centers and in establishing a progression from PanIN-1 to PanIN-2 to PanIN-3 to invasive cancer, there are problems with it. First, the assignment of lesions to the PanIN-2 category is not reproducible between pathologists, and second, morphologic analyses suggest a two-tier grading system might more accurately reflect the nuclear changes that occur in PanINs. Certainly, as is true in other organ systems, when the time comes that therapeutic decisions have to be made based on the grade of intraepithelial neoplasia, the development of a two-tier grading system will be needed. Such a two-tier system could combine PanIN-1 and PanIN-2 under the designation “low-grade PanIN” and leave PanIN-3 as “high-grade PanIN.” The second controversy, or at least a poorly defined area, in the study of PanINs is the significance of a PanIN lesion at a surgical margin. It is generally agreed that no therapy is needed for PanIN-1 or PanIN-2 at a margin. There have, however, been several case reports of PanIN-3 lesions progressing to invasive ductal adenocarcinoma. Therefore, the resection of additional pancreatic parenchyma to achieve a margin free of PanIN-3 may be warranted in some instances. We like to take the patient’s clinical situation into account when making the decision to resect additional pancreatic parenchyma. If patients have a large invasive cancer with multiple lymph node metastases, then their invasive cancer possesses a significantly greater threat to their life than a PanIN-3...
ever will. In these instances, we often recommend that no additional pancreas be resected. By contrast, if patients are young and have a potentially curable pancreatic lesion, the resection of additional parenchyma to achieve a margin free of PanIN-3 may be recommended.

### PANCREATIC INTRAEPITHELIAL NEOPLASIA VERSUS INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Both PanINs and IPMNs are intraductal epithelial neoplasms composed of mucin-producing columnar epithelial cells.31 Although the distinction between these two neoplasms is relatively easy at the extremes, there can be overlap. A meeting of international experts was recently held at the Johns Hopkins Hospital (Baltimore, MD) to define diagnostic criteria useful in distinguishing between PanINs and IPMNs.31 As summarized in Table 5, IPMNs are usually clinically detectable, grossly visible neoplasms that produce grossly visible mucin and well-formed papillae. In contrast, PanINs are usually not clinically detectable, are not grossly visible, and do not produce grossly visible mucin.31 PanINs do not form tall well-formed papillae, and they do not express MUC2. MADH4/DPC4 is inactivated in about one-third of PanIN-3 lesions, and PanINs are associated with ductal/tubular-type invasive adenocarcinoma.

Finally, the intestinal-type IPMN is clearly distinguished from the previous two pathways in that it can progress to invasive colloid-type invasive adenocarcinoma, a form of invasive cancer associated with better prognosis than the more common tubular/ductal type of invasive adenocarcinoma.

### EARLY DETECTION

The noninvasive precursor lesions discussed in this review are certain to grow in importance as we define groups of patients with a significantly increased risk of developing pancreatic cancer and as our ability to image smaller and smaller lesions in the pancreas improves.119,120 For example, individuals with a strong family history of pancreatic cancer and individuals with the Peutz–Jeghers syndrome have been shown to have an increased risk of developing pancreatic cancer; M. Canto et al. have developed a research protocol to screen these patients for early pancreatic cancer using EUS.120 Remarkably, a number of asymptomatic IPMNs have been detected and resected in these patients.

It is critical that these noninvasive lesions be detected and treated, because even small (<1-cm) invasive cancers usually prove lethal.121,122

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