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## INTRADUCTAL TUBULOPAPILLARY NEOPLASM OF THE PANCREAS: A CLINICOPATHOLOGIC AND IMMUNOHISTOCHEMICAL ANALYSIS OF 33 CASES

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### Abstract

**Background**—Intraductal tubulopapillary neoplasm (ITPN) is a relatively recently described member of the pancreatic intraductal neoplasm family. Thus, the literature on its histologic and immunohistochemical features, clinical behavior, and its similarities and differences from other pancreatic neoplasms is limited.

**Design**—Thirty-three cases of ITPN, the largest series to date, were identified. Immunohistochemical labeling for cytokeratins, glycoproteins, pancreatic enzymes, markers for intestinal and neuroendocrine differentiation, and antibodies associated with genetic alterations previously described in pancreatic neoplasms were performed. Clinicopathologic features and survival was assessed.

**Results**—Seventeen patients were female, fourteen were male. Mean age was 55 years (range, 25–79). Median overall tumor size was 4.5 cm (range, 0.5–15). Forty-five percent of the tumors occurred in the head, 32% in the body/tail, and 23% showed diffuse involvement. Microscopically,

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the tumors were characterized by intraductal nodules composed of tightly packed small tubular glands lined by cuboidal cells lacking apparent mucin. Although it was often challenging to determine its extent, invasion was present in 71%. Almost all tumors labeled for CAM5.2, CK7 and CK19; most expressed CA19.9, MUC1 and MUC6. CDX2, MUC2, trypsin, chymotrypsin, chromogranin and synaptophysin were not expressed. SMAD4 expression was retained in 100%, p16 expression and p53 overexpression was seen in 33% and 27%. Follow-up information was available for twenty-two patients (median follow-up, 45 months; range, 11–173). Two patients with invasive carcinoma died of disease at 23 and 41 months. One patient died of unrelated causes at 49 months. Twelve patients were alive with disease. Seven patients were alive with no evidence of disease. The overall 1-, 3- and 5-year survival rates were 100% in patients without an invasive component and 100%, 91% and 71% in patients with an invasive component (p=0.7).

**Conclusions**—ITPN is a distinct clinicopathologic entity in the pancreas. Despite the difficulties of determining the extent of invasive carcinoma in many cases, the overall outcome appears relatively favorable and substantially better than that of conventional ductal adenocarcinoma, even when only the cases with invasive carcinoma are considered.

## INTRODUCTION

Since the first description more than three decades ago<sup>1</sup>, intraductal papillary mucinous neoplasm (IPMN) of the pancreas has become widely recognized as one of the most common cyst-forming pancreatic neoplasms, and several variants of intraductal neoplasms have been described including the gastric, intestinal, or pancreatobiliary subtypes<sup>2–9</sup>. All IPMNs have variable papilla formation and produce mucin, but each subtype has certain distinctive histologic, immunohistochemical and genetic features. These tumors also exhibit a variable degree of cytoarchitectural atypia (low-grade and high-grade)<sup>6</sup> and may be associated with different types of invasive carcinoma (tubular or colloid)<sup>2, 10–17</sup>. The current (2010) World Health Organization designate “intraductal oncocytic papillary neoplasm (IOPN)<sup>18</sup>” neoplasm as one of the subtypes of IPMN, as well<sup>8</sup>. However, there are many differences between these entities arguing against this classification including their distinct molecular features<sup>19</sup>, and biologic behavior<sup>20, 21</sup> compared to other subtypes of IPMN.

Recently, another intraductal neoplasm with a distinctive pattern of growth has been described<sup>8</sup>: Intraductal tubulopapillary neoplasm (ITPN) has minimal papilla formation, instead filling the ducts with back-to-back tubular glands, and is not associated with extensive luminal or intracellular mucin accumulation<sup>8</sup>. However, the literature on ITPN is still very limited, due to the rarity of this disease. Our current understanding of this neoplasm is mainly based on individual case reports, analyses of small series or a metaanalysis of the literature<sup>22–36</sup>. The diagnostic criteria have also been poorly defined, leading to inconsistent pathologic classification and overlap with the pancreatobiliary subtype of IPMN.

Herein, we present the largest clinicopathologic studies of ITPN in an effort to more fully define the histologic and immunohistochemical features, clinical behavior, and similarities and differences from IPMNs as well as other pancreatic neoplasms.

## MATERIALS AND METHODS

The surgical pathology and consultation files of Memorial Sloan Kettering Cancer Center (New York, NY), Emory University School of Medicine (Atlanta, GA), University of Verona and Negrar Hospital (Verona, Italy), IPATIMUP (Porto, Portugal), and Technical University (Munich, Germany) were searched for cases of grossly visible intraductal pancreatic neoplasms with a predominantly tubular growth pattern and minimal mucin production, with or without an associated invasive adenocarcinoma component. Available gross photographs and descriptions as well as all histologic sections were re-evaluated to confirm the diagnosis and further characterize the spectrum of histology findings. Available medical records, including imaging study reports, were reviewed to obtain clinical data including age, gender, presenting symptoms, treatment, and outcome; for the consultation cases, contributing physicians were contacted.

Representative formalin-fixed paraffin-embedded tissue sections of each case, for which a paraffin block or unstained sections were available, were immunolabeled using the standard avidin-biotin peroxidase method. The following general groups of immunohistochemical stains were performed: keratins; glycoprotein markers; pancreatic enzymes, intestinal, hepatocellular, and neuroendocrine differentiation markers; and antibodies associated with genetic alterations previously described for other pancreatic neoplasms. The antibodies used along with their sources, dilutions, and pretreatment conditions are listed in Supplemental Table 1. The controls used were as follows: benign and neoplastic pancreatic tissue for CAM5.2, CK7, CK19, B72.3, CA125, CA19.9, monoclonal CEA, trypsin, chymotrypsin, chromogranin, synaptophysin, SMAD4,  $\beta$ -Catenin and E-Cadherin; benign and neoplastic colon tissue for MUC2 and CDX2; benign gastric mucosa for MUC5AC and MUC6, benign liver for HepPar-1; and colonic adenocarcinoma for p53.

For all antibodies, labeling in at least 10% of cells was considered to be expression (labeling in 10–25% of cells was considered to be focal). For p53 and CDX2, only nuclear labeling was regarded as expression. For SMAD4, loss of labeling in the face of retained labeling in non-neoplastic nuclei was regarded to be abnormal. For E-cadherin, loss of the normal cell membrane pattern and for  $\beta$ -catenin, an alteration from the normal cell membrane pattern to nuclear labeling was considered abnormal.

### Statistical Analysis

Mean, median and ranges were used to describe quantitative variables. The 1-, 3-, and 5-year survivals were retrieved from Life Tables. Kaplan-Meier survival curves and the log-rank test were used for survival analyses. For all analyses, the IBM-SPSS version 20.0 was used, and the threshold for statistical significance was set at  $P < 0.05$ .

## RESULTS

We identified a total of thirty-three cases that met the criteria for ITPN described above. The clinicopathological features of the cases analyzed are summarized in Tables 1 and 2.

## Clinical Findings

The patients included seventeen females and fourteen males; the gender was unknown for two cases. Patients' ages ranged from 25 to 79 years (mean=55 years). Presenting symptoms included abdominal pain, nausea, vomiting, steatorrhea, and weight loss. None of the patients presented with jaundice. Five patients had experienced prior episodes of acute pancreatitis. Two patients had diabetes mellitus. One patient had been treated for cholangiocarcinoma, diagnosed three years prior to ITPN. Another patient had a family history of pancreas cancer, although detailed family history data were not known for most of the cases.

The neoplasms were distributed throughout the gland, 45% were located in the head, 32% in the body/tail, and 23% diffusely involved the gland. Both solid and cystic regions within each case were seen on cross-sectional imaging. In five cases (mostly those involving the head of the gland), the intraductal nature of the lesion was specifically recognized on pre-operative imaging as duct of Wirsung dilatation, with a stated differential diagnosis of IPMN. Other cases were reported as partially cystic masses.

All but two patients were treated primarily by surgical resection; two patients only underwent biopsy of an intraductal polypoid mass due to co-morbid illnesses. None of the patients received neoadjuvant chemotherapy and two patient with recurrences received chemotherapy.

## Pathologic Findings

Grossly, the tumors ranged from 0.5 to 15 cm (median=4.5 cm) in greatest dimension. Of the fifteen cases for which detailed gross information was available, the intraductal nature of the tumor was specifically documented in only 60% of the cases. Fifty-three percent of the tumors were described as predominantly solid or polypoid lesions, some within the dilated ducts or cysts. One of these tumors consisted of a grossly circumscribed solid mass in the tail of the gland, with a finger-like projection extending into the main pancreatic duct (Figure 1). The remaining 47% were described as cystic or multicystic lesions. None of the cases was described to exhibit luminal mucin accumulation grossly. The stroma between the nodules and cysts was densely sclerotic.

Microscopically, the tumors consisted of variably sized circumscribed nodules of back-to-back tubular glands, resulting in large cribriform structures surrounded by fibrotic stroma (Figure 2). Papilla formation was seen only focally in 36% of the cases. The intraductal location was confirmed in every case by demonstrating focal continuity of the neoplastic epithelium with histologically normal-appearing ductal epithelium that either surrounded the tumor nodules or partially lined the cystic spaces into which the polypoid tumor masses projected (Figure 3). However, the majority of intraductal neoplastic proliferations expanded the ducts such that no residual non-neoplastic ductal epithelium remained along the lumen and some of these nodular tumor growths showed irregular contours with strands of cells extending into the surrounding pancreatic parenchyma with an associated stromal desmoplastic reaction. The size of the individual nodules ranged from microscopic (corresponding to the diameter of medium-sized interlobular ducts) to one case in which an

individual cyst measured 10 cm. Thus, in many cases, the intraductal proliferation appeared to extend from the major pancreatic ducts into smaller secondary ducts, with each involved ductal profile appearing as a separate tumor nodule in cross section. In 58% of the cases, multiple prominent lymphoid aggregates were identified around the tumor.

Within the tumor nodules, there were tightly packed small glands lined by predominantly cuboidal cells with minimal to modest amounts of eosinophilic to amphophilic cytoplasm (Figure 4). Four cases revealed clear cell morphology, three focally, one extensively (Figure 5). Foci with amorphous acidophilic secretions were present in three cases (Figure 6). However, in all but cases, there was no or only minimal intracellular mucin; only one case with more columnar tumor cells revealed some intracellular mucin (this case revealed all the other characteristic features of ITPN). The nuclei were round to oval and moderately to markedly atypical. Some cases had centrally located, single, prominent nucleoli. Mitotic figures were readily identifiable. Also, the majority (64%) of the cases showed necrosis within the tumor nodules, often with comedo-like pattern (Figure 7). Some tumors also had hypercellular, desmoplastic stroma within the center of the tumor nodules, although the nodule periphery remained circumscribed. Of note, one tumor revealed calcifications with ossification.

Because many of the tumor nodules lacked a peripheral rim of non-neoplastic ductal epithelium, it was often very difficult to determine whether invasive carcinoma was present, and even for cases with established invasive carcinoma, it was challenging to determine its extent. Foci in which there were thin strands of cells extending away from the edges of the nodules were interpreted to represent stromal invasion (Figure 8A). In a few cases there were individual malignant glands clearly infiltrating into the stroma (Figure 8B). In two cases, the presence of invasion could not be assessed due to the biopsy nature of the specimens. Of thirty-one resections, nine (29%) cases had no definite invasive carcinoma in the slides available for review. Twenty-two (71%) cases had invasive carcinoma components that were ranged from minute (representing less than 10% of the tumor, n=12) to substantial (10%–50% of the tumor, n=7) to extensive (more than 50% of the tumor, n=3). Three cases had lymphovascular invasion, and three had perineural invasion. Of known sixteen cases, none had lymph node metastases.

Adjacent uninvolved pancreatic parenchyma was either normal or atrophic with islet aggregation. Features of chronic pancreatitis were not identified. There was infrequent pancreatic intraepithelial neoplasia (PanIN), and in every instance, the PanIN was low-grade. One case also revealed an incidental neuroendocrine microadenoma.

### Immunohistochemical Findings

The results of the immunohistochemical studies are summarized in Table 3.

All tested tumors labeled with CAM5.2, and CK7; 89% labeled with CK19. In contrast, only 19% of the tumors contained rare, scattered cells that labeled with CK20, and in one of these tumors, rare scattered cells also labeled with CDX2. Ninety-three percent of the tumors labeled with CA19.9, which is typically expressed in ductal epithelial cells and ductal neoplasms. Monoclonal CEA was also expressed in half of the cases. Tumor-specific

glycoproteins were less consistently expressed, ranging from 14% of the tumors focally labeling with CA125 to 29% diffusely labeling with B72.3. The MUC family of proteins showed a fairly consistent pattern of labeling, with 88% and 68% of the tumors expressing MUC1 and MUC6 (Figure 9), respectively but none expressing MUC2. Similarly, ITPNs were consistently negative for MUC5AC, except one tumor with focal MUC5AC expression. Of note, this case was otherwise a typical ITPN; therefore it was not excluded from the study.

There was no expression of the pancreatic enzymes, trypsin and chymotrypsin in any of the tumors and only one tumor focally expressed HepPar-1. In contrast to other ductal neoplasms of the pancreas, scattered chromogranin and synaptophysin positive cells were identified very rarely (4%). Among antibodies associated with genetic alterations previously described in other pancreatic neoplasms, SMAD4 loss occurred in none of the ITPNs, and p16 expression and nuclear p53 accumulation were found in only 33% and 27%, respectively. Similarly, E-Cadherin expression was normal (membranous) in all and only one revealed abnormal (nuclear)  $\beta$ -Catenin reactivity.

### Clinical Outcome

Clinical follow-up information was available for twenty-two cases, with a median follow-up of 45 months (range, 11–173). Only two patients with invasive carcinoma died of disease at 23 and 41 months, respectively. Twelve patients were alive with disease, with a median follow-up of 61.5 months (range, 12–173). Of these, four patients had histologically proven local recurrences (one also had liver metastasis), and another two had liver metastases after 5 to 72 months. At the time of last follow-up, seven patients were alive with no evidence of disease, with a median follow-up of 19 months (range, 11–95). One of these patients, treated initially by pancreatoduodenectomy, was found to have dilated ducts in the pancreatic remnant, radiographically suspicious for recurrence; however, completion pancreatectomy showed only ductal ectasia without evidence of the neoplasm. One patient died of unrelated causes at 49 months.

The overall 1, 3- and 5-year survival rates were 100, 93 and 77%, respectively. The overall 5-year survival rate was 100% in patients without an invasive component and 1, 3- and 5-year survival rates were 100%, 91% and 71%, respectively in patients with an invasive component ( $p=0.7$ ) (Figure 10). Attempts to correlate the clinical outcome with the extent of invasive carcinoma were failed as the patient with the greatest volume of invasive carcinoma (representing more than 50% of the tumor) was free of disease at 173 months, whereas one of the two patients who died of disease had a minute invasive carcinoma (representing less than 10% of the tumor). More confusing was the fact that two patients without identifiable invasive carcinoma had recurrence of disease, although only limited slides from the primary presentation were available for review in these cases.

### DISCUSSION

With intraductal papillary mucinous neoplasms (IPMNs) as the prototype, the family of intraductal neoplasms of the pancreas includes a variety of architectural patterns and cytologic variants<sup>7, 8</sup>. Some of these are simply regarded as subtypes of IPMNs<sup>2-6</sup>. IOPN is

more distinctive<sup>18–21, 37–39</sup>; however, the current (2010) WHO designated this neoplasm to be a subtype of IPMN (“oncocytic type”) as well<sup>8</sup>. In the last couple of decades, IPMNs have been subjected to detailed studies, results of which have enormously added to our knowledge of IPMNs<sup>2–6, 10–14, 16, 17</sup>. However, experience with ITPN is limited.

In this study, we analyzed thirty-three cases. All of our patients are adults (mean age=55 years) and there is a slight female predominance (F:M=1.2). Like IPMNs, ITPNs most commonly involve the head of the pancreas but may also arise in the tail or involve the entire gland. Recently a case of multifocal ITPN has also been reported<sup>33</sup>. The degree of ductal dilation varies somewhat, with some cases showing only minimally dilated ducts due to the extensive obliteration of the ductal lumina. Most patients presented with symptoms of pancreatitis, abdominal pain or sense of fullness. Jaundice is distinctly unusual and lacking in all patients in our series. Similarly, in their metaanalysis of publications on surgically resected ITPN, Date et al. identified only 3 cases with jaundice<sup>36</sup>.

Microscopically, most ITPNs show a predominant or exclusive tubular growth pattern, and despite the entity’s name, true papilla formation is seen only focally in 36% of the cases. Some regions of the intraductal tumor grow as solid sheets of cells with minimal lumen formation. This pattern has also been observed in IOPN<sup>18, 21</sup>. In contrast to the abundant mucinous cytoplasm that characterizes many cases of IPMN<sup>3, 7, 8</sup>, there is usually no obvious intracellular mucin in ITPNs. Predominantly cuboidal tumor cells reveal minimal to modest amounts of eosinophilic to amphophilic and rarely clear cytoplasm (12% of our cases). Recently, Ahls et al. also reported an ITPN with clear cell phenotype<sup>29</sup>. Rare cases of ITPN with extensive calcification<sup>35</sup> or stromal osseous and cartilaginous metaplasia<sup>28</sup> have also been described, similar to one of our cases with calcification and bone formation. Nuclear atypia varies from moderate to marked, and mitotic figures are easily identified. Some cases have necrosis within the intraductal component and others demonstrate foci of stromal desmoplasia. The presence of these features of high grade dysplasia, along with the absence of residual benign ductal epithelium surrounding many of the tumor nodules, conspire to make the recognition of the intraductal nature of these neoplasms very difficult. In fact, on high power examination where the circumscribed contours of the tumor nodules are not apparent, it is easy to mistake the intraductal foci for highly cellular invasive carcinoma, although the architectural and cytologic differences from most cases of conventional pancreatic ductal adenocarcinoma are striking.

Invasive carcinomas arising in association with ITPNs typically consist of individual cells or small, angulated non-mucinous glands extending away from the periphery of the involved ducts into the surrounding desmoplastic stroma (Figure 8). The extent of invasive carcinoma can be very difficult to assess, but in approximately one-third of our cases, there was substantial to extensive invasive carcinoma that was relatively easy to recognize. In 39% of the cases there were irregularities in some of the tumor nodules that we interpreted as focal invasive carcinoma. The remaining cases showed no evidence of invasion.

Despite the presence of invasive carcinoma in approximately two-thirds of the cases, the overall outcome appears to be quite favorable. Previously, lymph node and liver metastases were rarely reported<sup>34</sup>. In our series, of twenty-two patients with available follow up

information, only two patients (9%) died of disease and six others (27%) suffered from recurrences or metastases and among the recurrences were a few patients with minute invasive carcinoma. Thus, it appears that there exists a potential for progression even in the absence of obvious widespread invasive carcinoma or, more likely, the presence of invasion can be morphologically so subtle that it is difficult to accurately quantify.

Immunohistochemically, ITPNs share ductal differentiation with IPMNs, and with most other pancreatic neoplasms, by labeling with wide-spectrum (CAM5.2) and specific (CK7 and CK19) cytokeratin antibodies as well as expressing certain glycoproteins including B72.3, CA19.9, and monoclonal CEA. However, most ITPNs do not label with CA125. Similarly, nuclear p53 accumulation, which is found in 60% of pancreatic ductal adenocarcinomas and in 0–38% (weighted mean, 21%) of IPMNs, – usually with high-grade dysplasia or invasive carcinoma<sup>40–42</sup> – is only seen in 27% of ITPNs. SMAD4 is also normally expressed (retained) in ITPNs. This contrasts with loss of expression in 55% of ductal adenocarcinomas, although non-invasive IPMNs also typically have normal patterns of SMAD4 expression<sup>7, 43</sup>.

The expression patterns for MUCs have been correlated with the direction of differentiation of pancreatic neoplasms towards normal cell counterparts of the gastrointestinal tract<sup>4, 12, 44–47</sup>. MUC1 is expressed in almost all examples of pancreatobiliary type neoplasms, including ductal adenocarcinomas and pancreatobiliary subtype IPMNs, and its expression has been associated with increased metastatic ability of pancreatic cancer cell lines<sup>48–50</sup>. MUC6 is expressed in ductal adenocarcinomas, pancreatobiliary type IPMNs, IOPNs and serous cystadenomas<sup>51, 52</sup>. MUC5AC is widely expressed in ductal adenocarcinomas, all subtypes of IPMNs (gastric, intestinal, and pancreatobiliary), and IOPNs<sup>4</sup>. Finally, expression of MUC2 (and CDX2) defines the intestinal pathway of differentiation, characteristic of intestinal subtype of IPMNs and associated colloid carcinomas<sup>4, 12</sup>. In our series of ITPN, MUC1 and MUC6 were expressed, whereas MUC2 and MUC5AC were not. Previous studies analyzing single cases or small series have also reported similar results<sup>22–36</sup>, except one case in which MUC5AC is reported to be positive<sup>53</sup>.

The expression of MUC1 and MUC6 suggests that ITPN has pancreatic (ductal) and possibly also gastric pyloric gland differentiation. The lack of MUC5AC points to an absence of gastric foveolar differentiation, which contrasts with the common expression of this marker in IPMNs<sup>4, 11, 54</sup>. Finally, the lack of intestinal differentiation in ITPNs is also reflected in the absence of MUC2 (and for CDX2) expression. Thus, it appears that ITPN lacks the gastroenteric differentiation seen in IPMN, and instead shows pancreatic duct differentiation morphologically and immunohistochemically.

A detailed study we performed recently on the genetic features of ITPNs has shown that ITPN is genetically distinct from IPMN and ductal adenocarcinoma, as it does not harbor the vast majority of the previously reported IPMN or ductal adenocarcinoma-related mutations<sup>55</sup>. The most important genotypic difference from IPMN and ductal adenocarcinoma is the absence of *KRAS* and *BRAF* mutations in ITPNs<sup>55</sup> (The vast majority of ductal adenocarcinomas harbor mutations of *KRAS*<sup>7</sup>. The adenocarcinomas



without mutations of *KRAS* often have mutations of *BRAF*<sup>56</sup>. Pancreatic intraepithelial neoplasia and IPMN also frequently harbor mutations of *KRAS*<sup>7</sup>). Emerging studies analyzing a small number of cases for selected gene mutations have also reported predominantly similar results<sup>25, 26, 29, 31, 34, 53, 57–60</sup>. These findings provide support not only for the proposition that ITPN is a distinct pancreatic intraductal neoplasm with different morphologic features and biologic behavior, but also for the hypothesis that distinct genetic pathways of tumor development correspond to the characteristic morphologic patterns of these different neoplasms. Of note, Schlitter et al.'s recent molecular analyses of biliary counterparts of ITPN<sup>61</sup> have highlighted the low prevalence of alterations of the common oncogenic signaling pathways in these neoplasms as well<sup>62</sup>.

The differential diagnosis of ITPN includes other intraductal tumors such as IPMNs, IOPNs, as well as other pancreatic neoplasms that may rarely grow within the ducts (acinar cell carcinoma, pancreatoblastoma, and well differentiated pancreatic neuroendocrine tumors). Most other intraductal neoplasms have a fundamentally papillary architecture, allowing relatively easy separation of IPMNs from ITPNs<sup>13, 14, 38</sup>. IPMNs may have some limited tubular growth, especially at the periphery of the involved ducts, but complete expansion and obliteration of the ductal profiles by a tubular proliferation is unusual. Similarly, IOPN can exhibit a solid or tubular growth pattern but ITPN lacks the abundant granular eosinophilic cytoplasm of IOPN. The back-to-back tubules of ITPN, each of which has a relatively small lumen, closely simulate the pattern of acinar neoplasms<sup>63–67</sup>. Most acinar cell carcinomas are large solid lesions and demonstrate no involvement of the native pancreatic ducts. However, rare cases have been described in which an intraductal growth pattern is present either focally or extensively<sup>64, 68–70</sup>. Fortunately, immunohistochemistry is very helpful. Acinar cell carcinomas consistently express pancreatic enzymes such as trypsin, chymotrypsin, and lipase and generally lack expression of CK19<sup>63–67</sup>. ITPNs consistently fail to express pancreatic enzymes. Pancreatoblastomas, which occur predominantly in infants, are also fundamentally acinar neoplasms of the pancreas that rarely have an intraductal growth pattern<sup>66, 71</sup>. Again, the presence of acinar differentiation can be detected immunohistochemically, and pancreatoblastomas additionally have squamous nest that are helpful in their separation from ITPNs. Finally, well differentiated pancreatic neuroendocrine tumors can rarely show an intraductal growth pattern<sup>72–75</sup> but the characteristic diffuse staining for neuroendocrine markers can separate these from ITPNs<sup>72–75</sup>.

In summary, ITPN is a distinct clinicopathologic entity in the pancreas. By its intraductal nature, it resembles IPMNs and by its acinar pattern, mimics acinar cell carcinoma; however, it has several distinguishing characteristics. (1) no visible secreted mucin, (2) highly cellular complex intracellular tumor nodules showing predominantly tubular or cribriform patterns, (3) absence of intracytoplasmic mucin, (4) atypical nuclei, (5) absence of acinar and neuroendocrine differentiation, and (6) despite the histologic indicators of a high-grade malignancy and even an invasive carcinoma component, a relatively favorable overall outcome.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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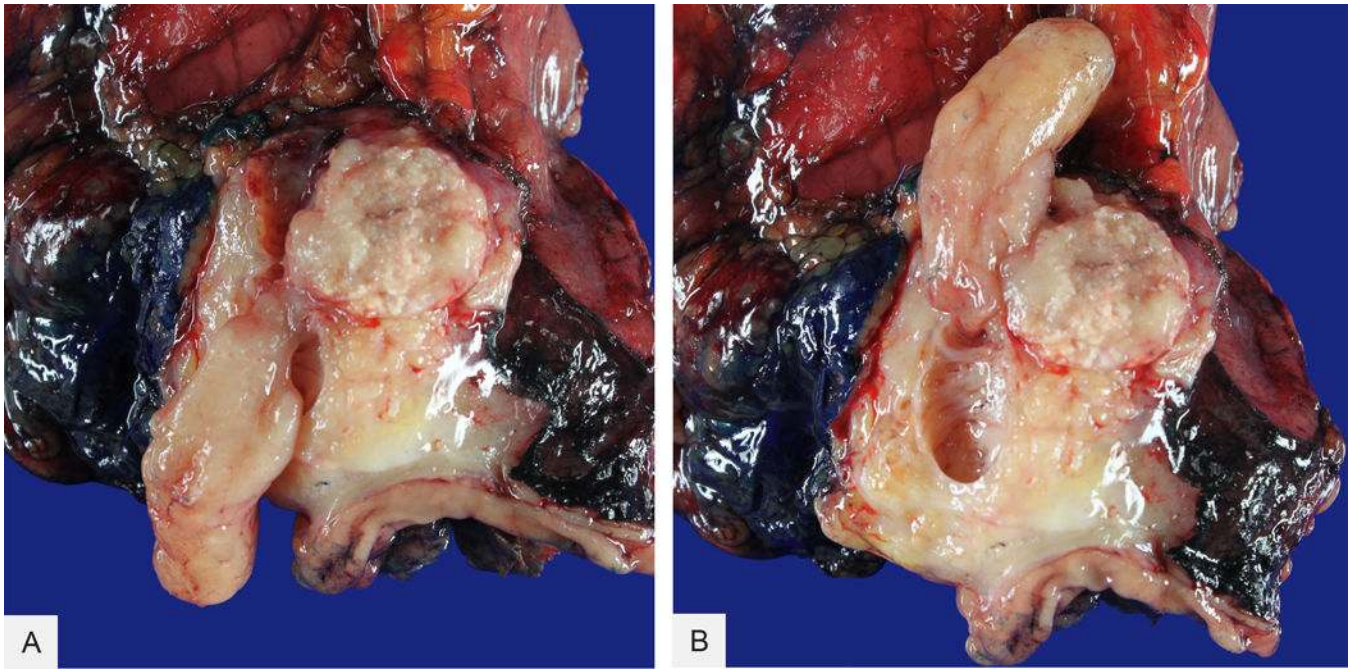
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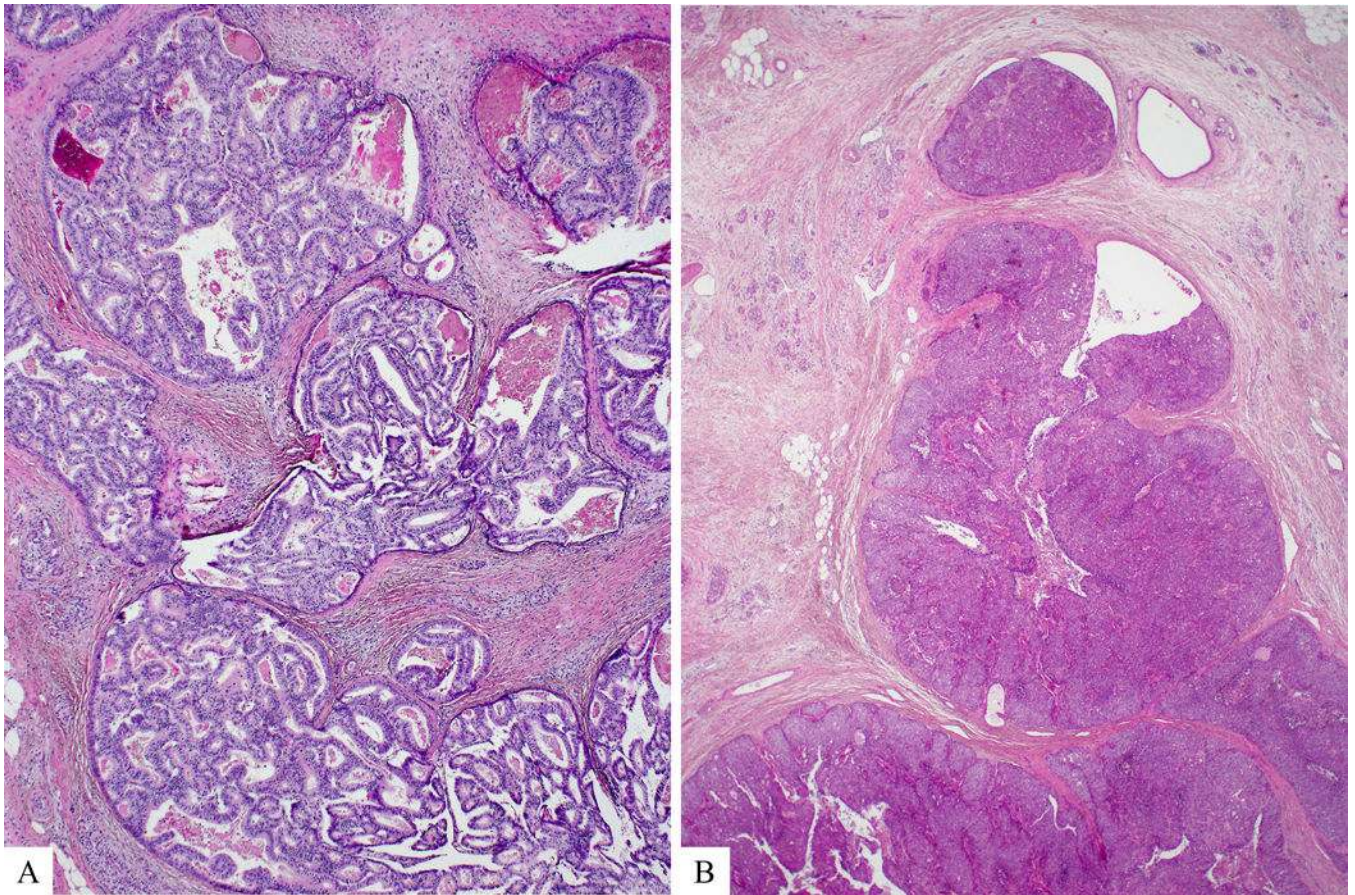
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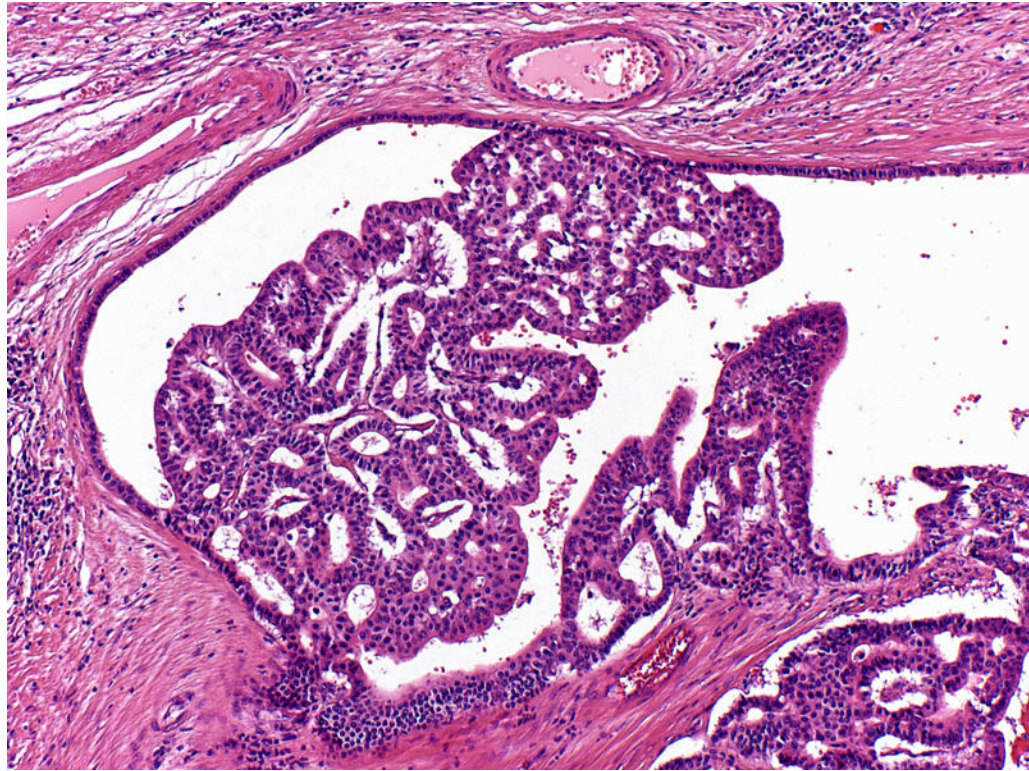


**Figure 1.**  
Intraductal tubulopapillary neoplasm, gross appearance. Note the polypoid component (A)  
within the main pancreatic duct (B)

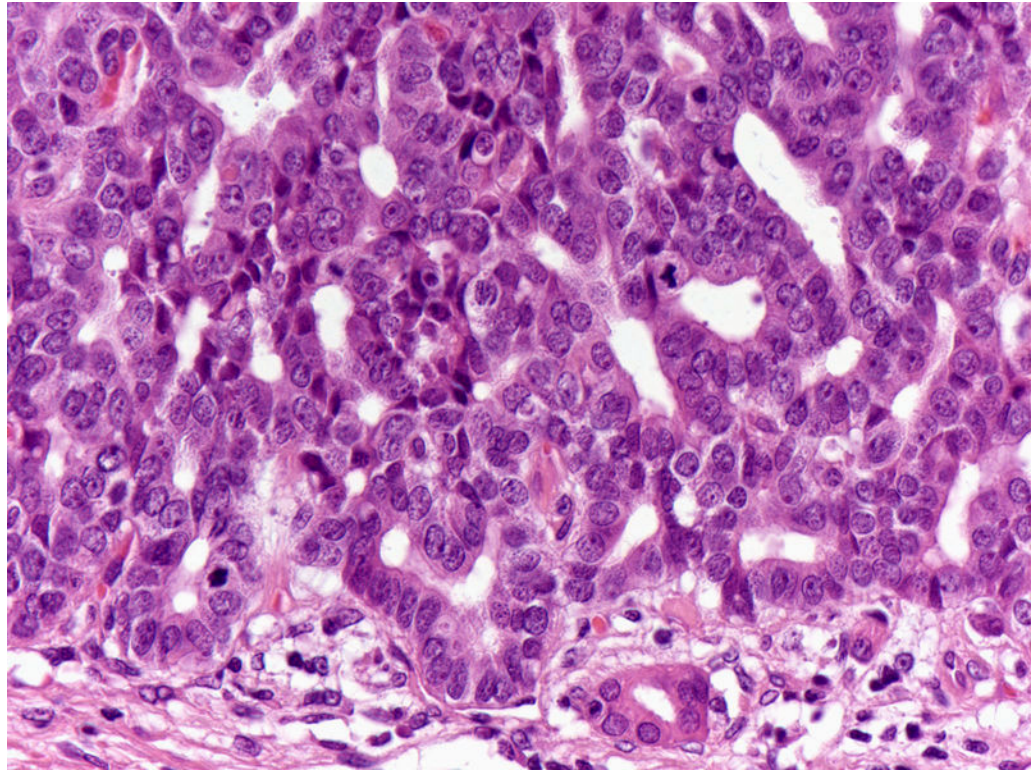


**Figure 2.** Microscopically, intraductal tubulopapillary neoplasm is characterized by nodules of back to back tubular glands, resulting in large cribriform structures within dilated pancreatic ducts (A). Solid areas with scattered abortive glandular arrangements may also be seen (B).

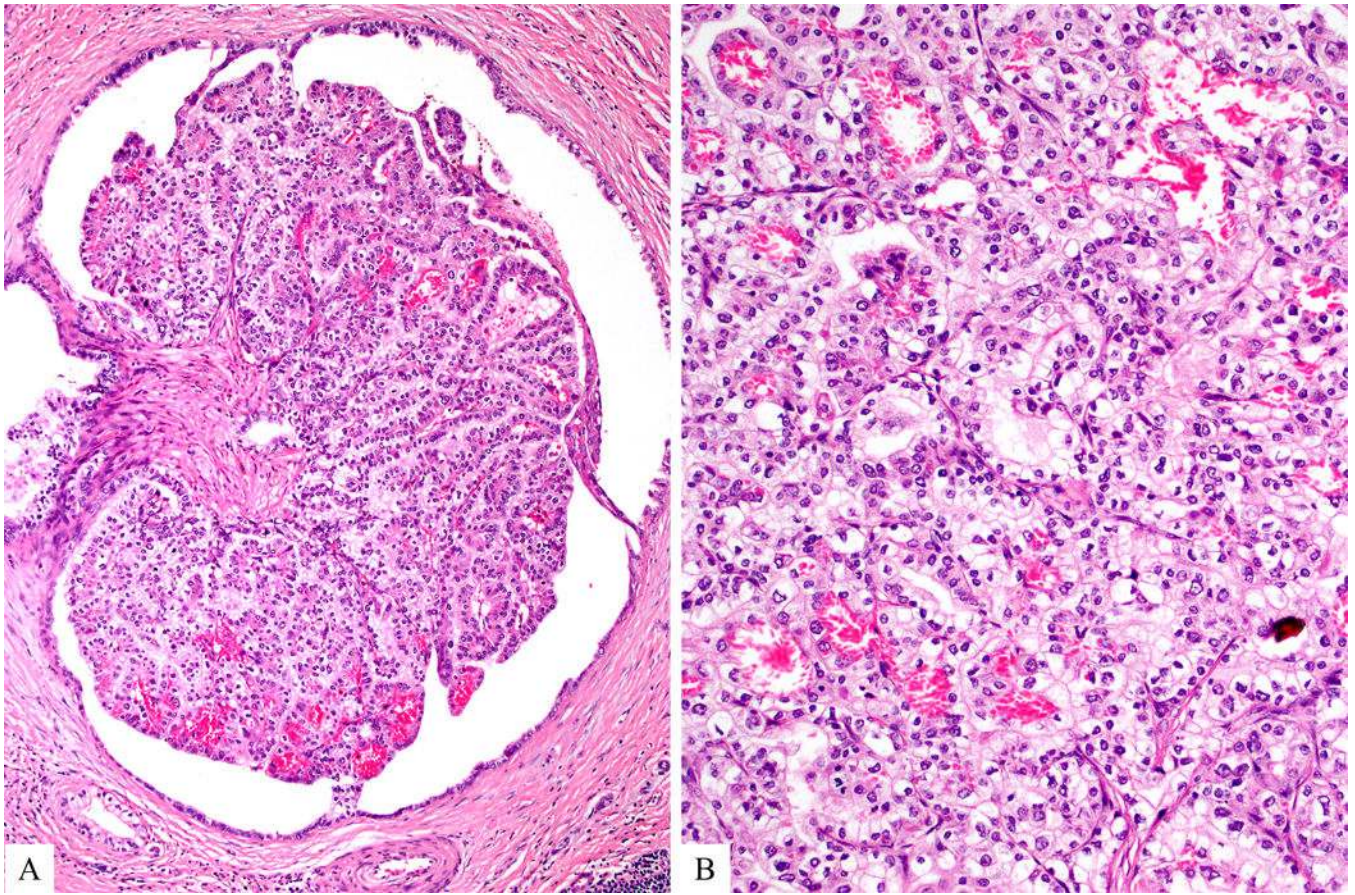




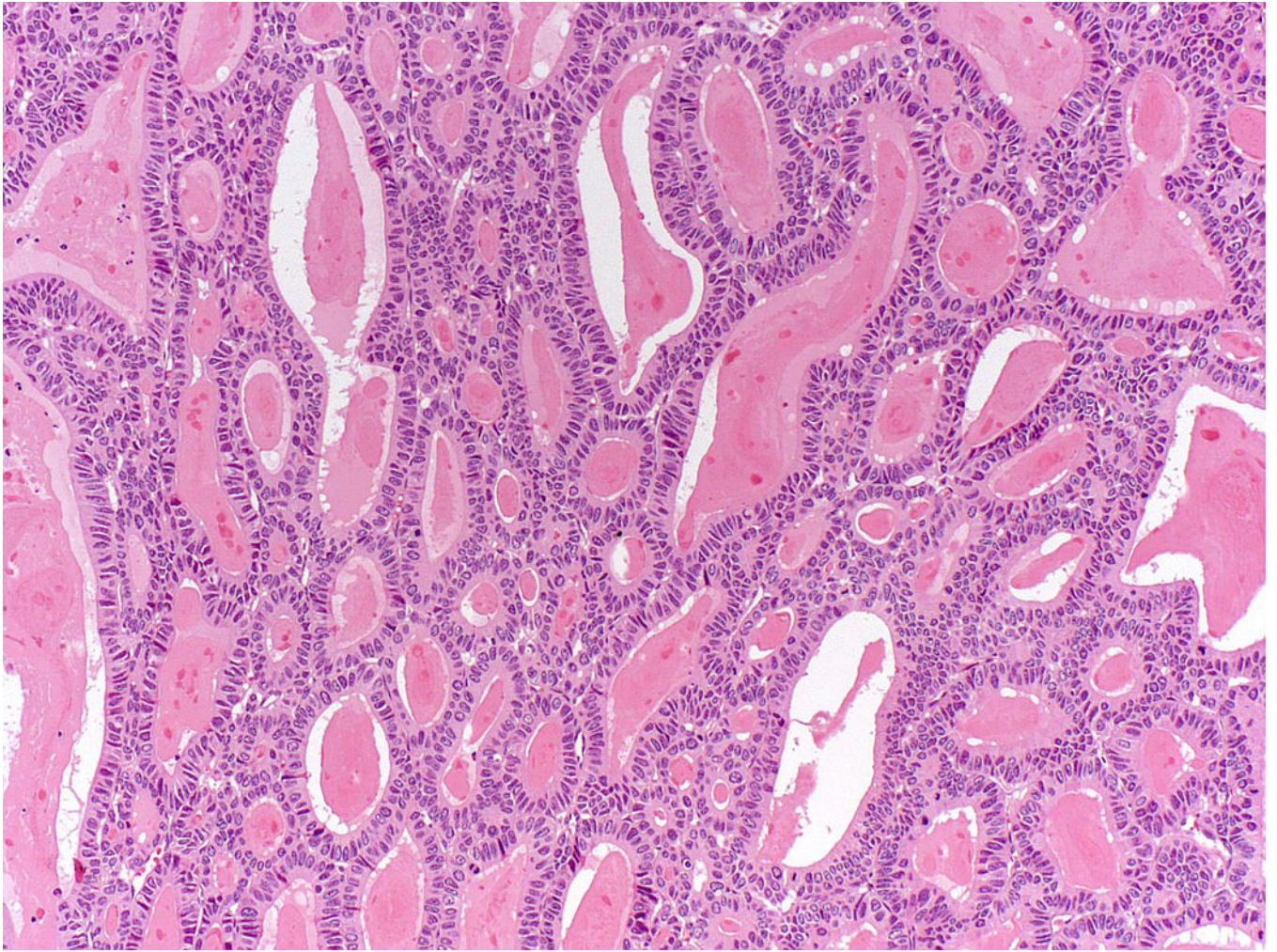
**Figure 3.** Continuity of the neoplastic epithelium with histologically normal-appearing ductal epithelium may be identified in some tumor nodules.



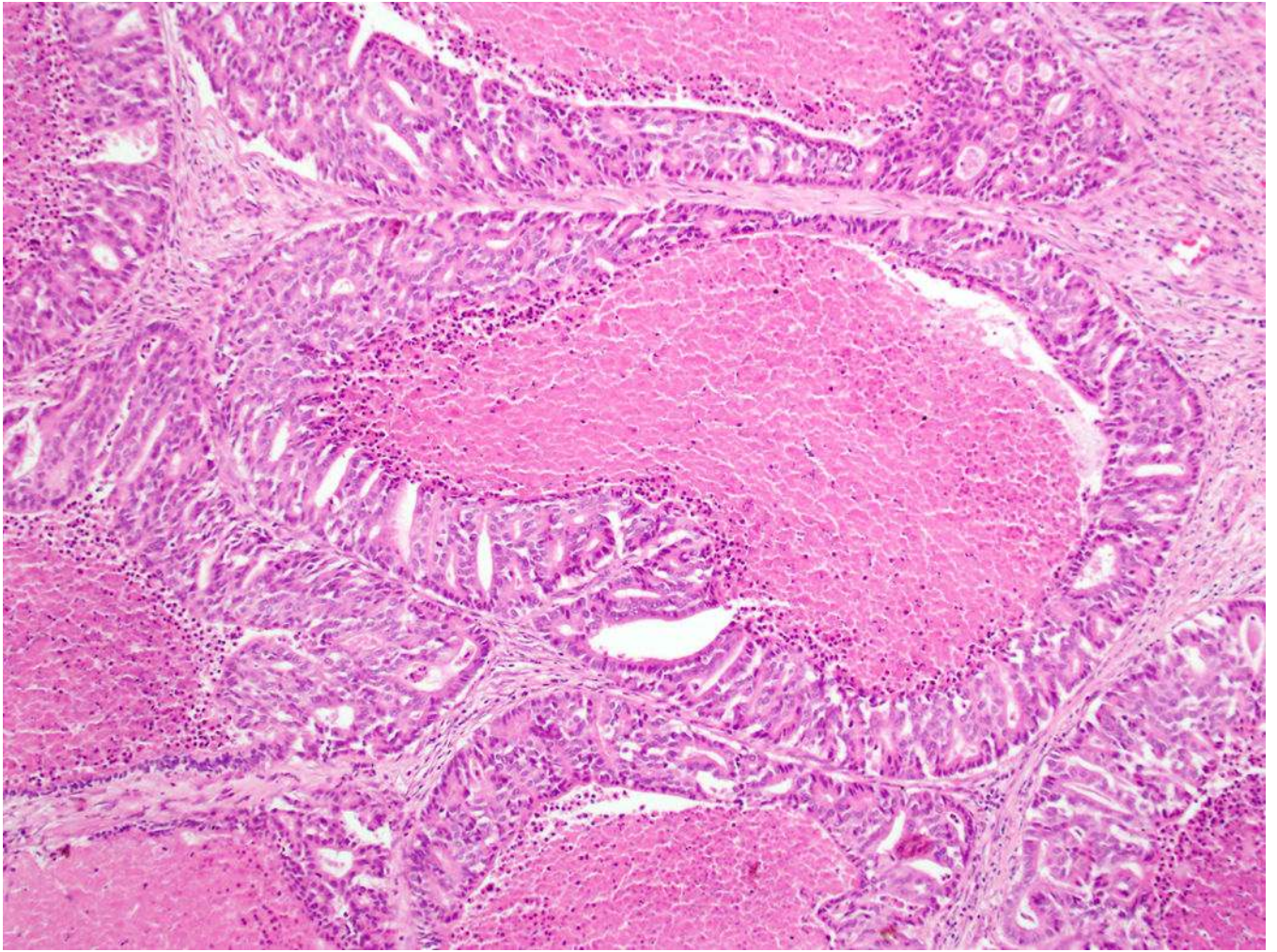
**Figure 4.** Tumor cells are cuboidal with modest amount of eosinophilic to amphophilic cytoplasm and round to oval atypical nucleus. Mitotic figures are easily identified.



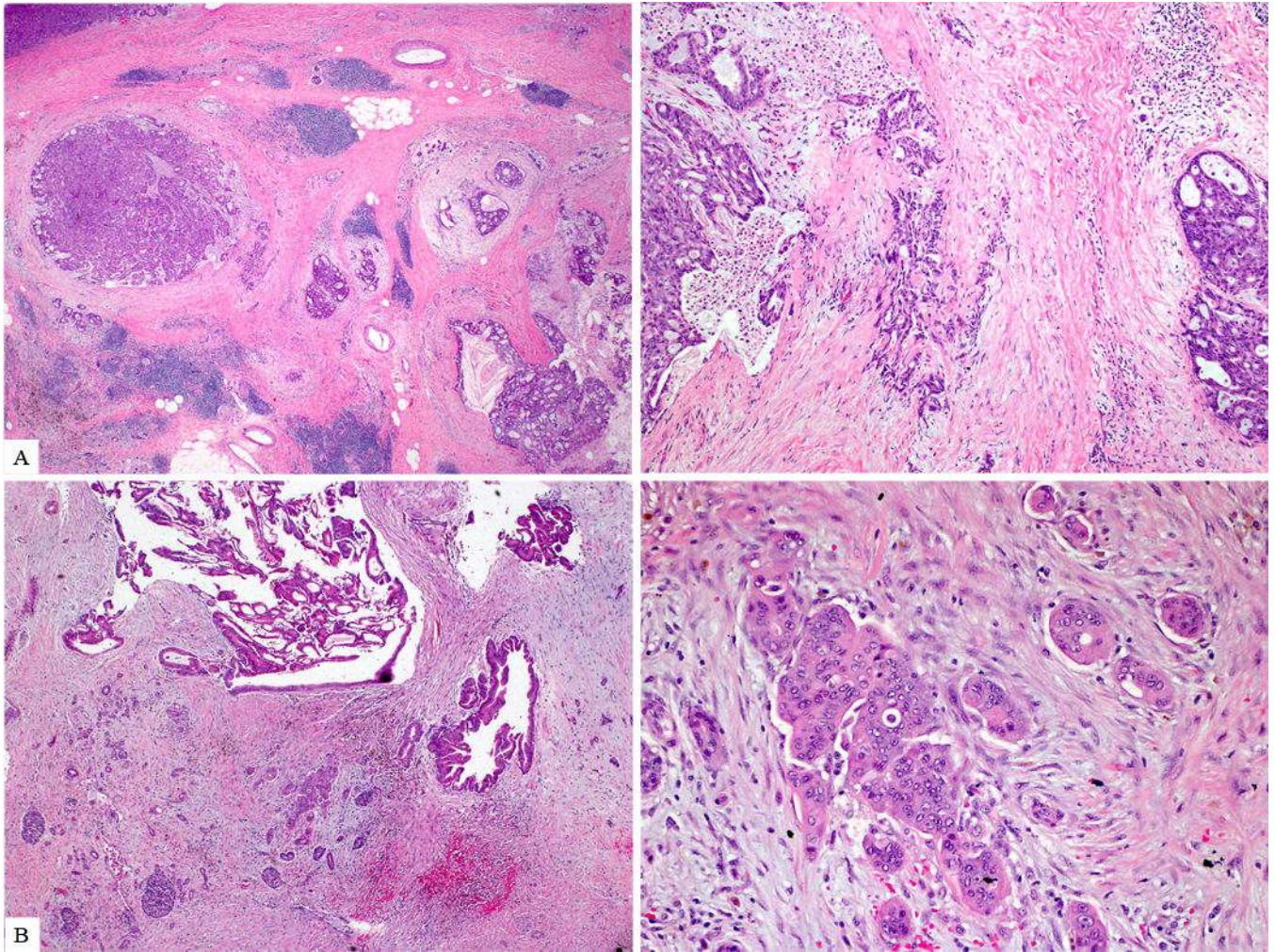
**Figure 5.**  
Rare cases may reveal focal or extensive clear cell morphology.



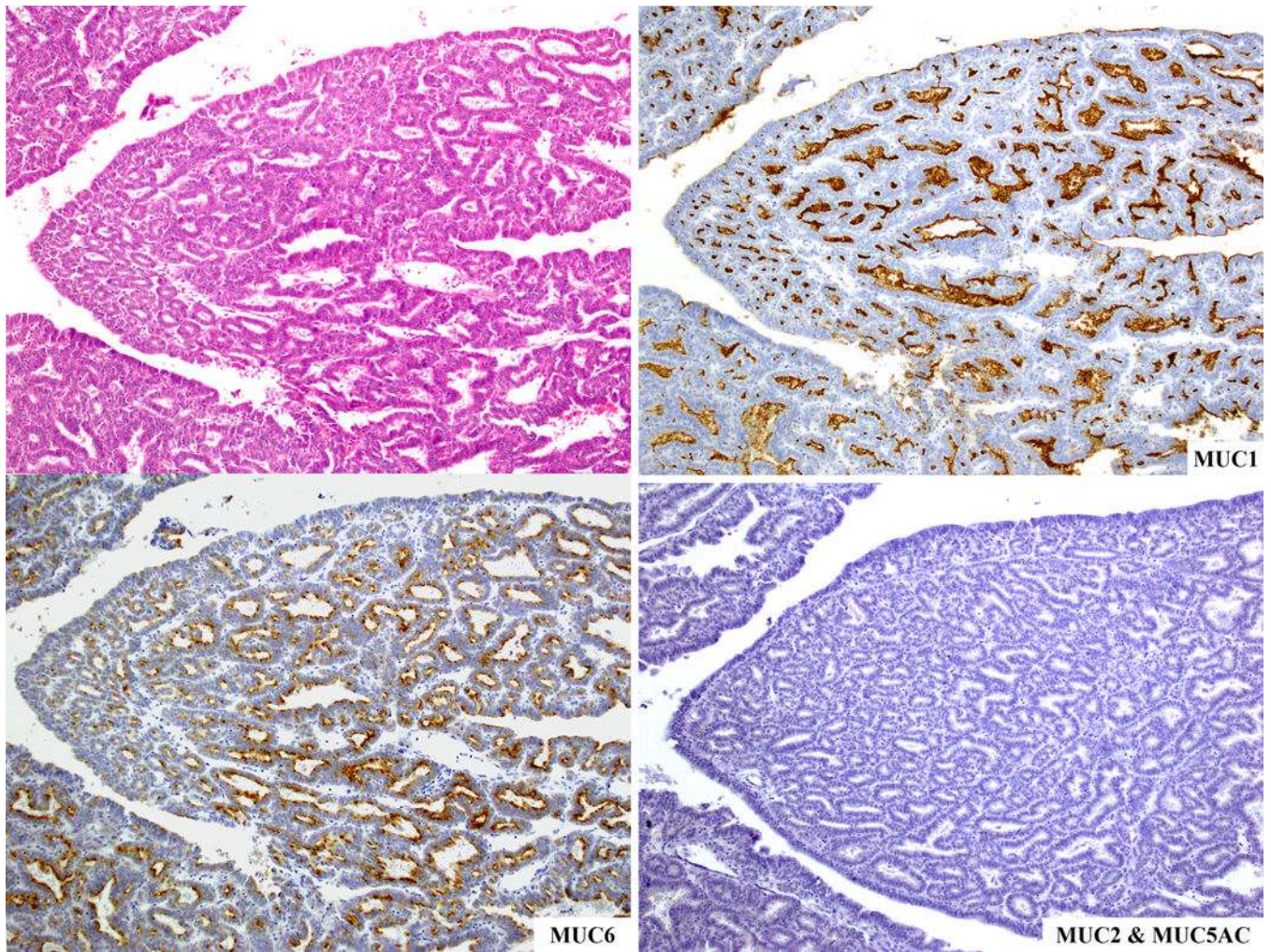
**Figure 6.** Intraluminal eosinophilic secretions may be seen but intracellular mucin is minimal/non-existent in intraductal tubulopapillary neoplasms.



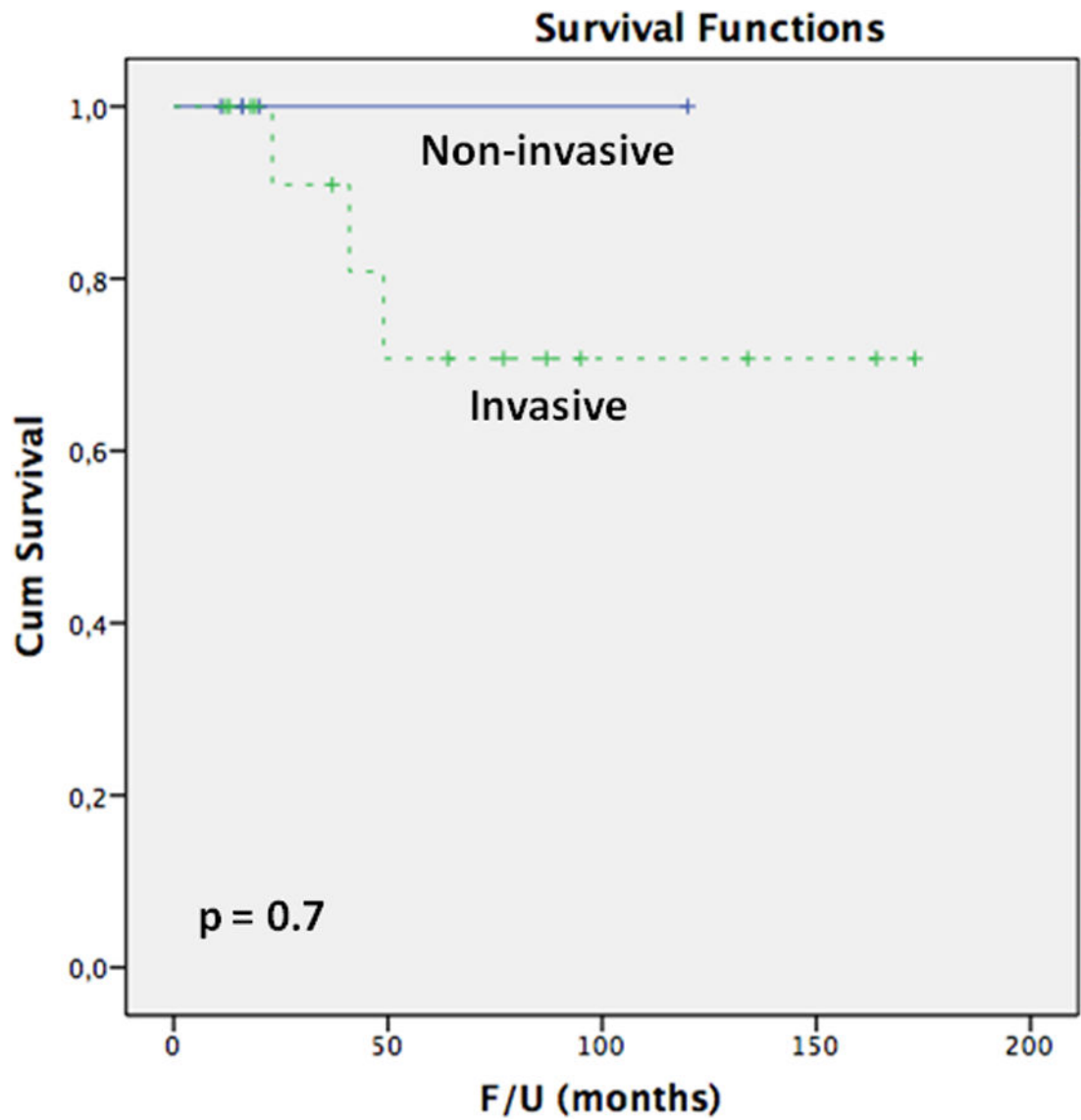
**Figure 7.**  
Necrosis within the tumor nodules, some with comedo-like pattern, is common.



**Figure 8.** Invasion, either in the form of individual/thin strands of cells extending away from the periphery of the involved ducts (A) or individual malignant glands clearly infiltrating (B) into the surrounding desmoplastic stroma, were identified in two third of the tumors.



**Figure 9.** The MUC family of proteins shows a fairly consistent pattern of labeling, with most cases staining for MUC1 and MUC6 but no cases expressing neither MUC2 nor MUC5AC.



**Figure 10.**  
The Kaplan-Meier analysis comparing the overall disease-specific survivals of patients without an invasive component and patients with an invasive component.



**Table 1**

Clinicopathologic features of the cases analyzed

	<b>n (%)</b>
<b>Mean age (range) (years)</b>	55 (25–79)
<b>Female/Male</b>	1.2
<b>Specimen type</b>	
<i>Total pancreatectomy</i>	5 (21)
<i>Pancreatoduodenectomy</i>	9 (38)
<i>Distal pancreatectomy</i>	8 (33)
<i>Biopsy</i>	2 (8)
<i>Unknown</i>	9
<b>Tumor location</b>	
<i>Head</i>	10 (45)
<i>Body</i>	1 (5)
<i>Tail</i>	6 (27)
<i>Diffuse</i>	5 (23)
<i>Unknown</i>	11
<b>Median overall tumor size</b>	4.5 cm
<b>Invasive component</b>	
<i>Present</i>	22 (71)
<10%	12
10–50%	7
>50%	3
<i>Absent</i>	9 (29)
<i>Unknown (Biopsy cases)</i>	2
<b>Papilla formation</b>	
<i>Present</i>	12 (36)
<i>Absent</i>	21 (64)
<b>Necrosis</b>	
<i>Present</i>	21 (64)
<i>Absent</i>	12 (36)
<i>Unknown</i>	
<b>Follow-up</b>	
<i>Mean follow-up (range) (months)</i>	60 (11–173)
<i>Median follow-up (range) (months)</i>	45 (11–173)
<i>No evidence of disease</i>	7 (32)
<i>Alive with disease</i>	12 (55)
<i>Died of disease</i>	2 (9)
<i>Died of other causes</i>	1 (4)
<i>Unknown</i>	11

**Table 2**

The clinicopathological features of the cases analyzed

Case	Age (year)	Sex	Symptom	Site	Size (cm)	Invasion (%)	Survival (month)	Outcome
1	51	F	Abdominal pain	Head	2.5	Yes (<10%)	41	DOD
2	63	F	Abdominal pain, steatorrhea	Diffuse	4.5	Yes (<10%)	49	DOC
3	53	F	Abdominal discomfort	Head	1.5	Yes (10–50%)	23	DOD
4	36	F	None	Diffuse	N/A	Yes (<10%)	134	AWD
5	65	F	Abdominal pain	Diffuse	N/A	No	16	AWD
6	25	F	None	Tail	10	Yes (<10%)	18	NED
7	61	M	Abdominal pain, weight loss	Head	8	Yes (<10%)	12	AWD
8	58	F	None	Tail	9	Yes (>50%)	173	AWD
9	72	F	None	Head	6	Yes (<10%)	87	AWD
10	38	M	None	Pancreatic duct	4	Biopsy only	51	AWD
11	53	M	Abdominal pain	Head	5.4	Yes (<10%)	164	AWD
12	45	M	Abdominal pain	Diffuse	0.5	Yes (<10%)	N/A	N/A
13	60	M	None	N/A	N/A	Yes (10–50%)	N/A	N/A
14	49	M	None	N/A	N/A	Yes (10–50%)	N/A	N/A
15	53	F	None	Head	5	Yes (<10%)	N/A	N/A
16	62	F	None	Diffuse	N/A	Yes (<10%)	N/A	N/A
17	N/A	N/A	None	N/A	N/A	No	N/A	N/A
18	56	F	Abdominal pain	Body	2.5	No	72	AWD
19	36	M	None	N/A	N/A	No	11	NED
20	71	F	None	Tail	5	No	120	AWD
21	53	M	None	Tail	2	Yes (10–50%)	95	NED
22	53	M	Abdominal pain	Pancreatic duct	N/A	Biopsy only	N/A	N/A
23	50	M	Abdominal pain	N/A	N/A	Yes (10–50%)	77	NED
24	73	F	Epigastric pain, nausea, vomiting	Tail	3.7	Yes (>50%)	64	NED
25	79	F	Abdominal pain, weight loss	Head	9	Yes (>50%)	37	AWD
26	75	M	N/A	Tail	1.5	No	20	AWD
27	64	M	Epigastric pain	Head	3	Yes (<10%)	19	NED

Case	Age (year)	Sex	Symptom	Site	Size (cm)	Invasion (%)	Survival (month)	Outcome
28	67	M	Abdominal pain	Head	3.5	Yes (10–50%)	13	NED
29	40	F	None	Head	3	No	N/A	N/A
30	57	F	None	N/A	1	No	16	AWD
31	N/A	N/A	None	N/A	N/A	No	N/A	N/A
32	53	F	None	N/A	6	Yes (<10%)	N/A	N/A
33	46	F	None	N/A	10	Yes (10–50%)	N/A	N/A

AWD: Alive with disease, NED: No evidence of disease, DOD: Died of disease, DOC: Died of other causes

N/A: Not available

**Table 3**

Results of the immunohistochemical studies

	Positive or Normal (%)	Negative or Abnormal (%)
<b>Keratins</b>		
Cam 5.2	12/12 (100)	0/12 (0)
CK 7	16/16 (100)	0/12 (0)
CK 19	16/18 (89)	0/18 (0)
CK 20	3/16 (19)*	13/16 (81)
<b>Glycoproteins</b>		
B72.3	2/7 (29)	5/7 (71)
CA125	2/14 (14)&	12/14 (86)
CA19.9	13/14 (93)	1/14 (7)
mCEA	6/12 (50)	6/12 (50)
MUC1	15/17 (88)	2/17 (12)
MUC2	0/17(0)	17/17 (100)
MUC5AC	1/24 (4)&	23/24 (96)
MUC6	17/25 (68)	8/25 (32)
<b>Lineage Markers</b>		
CDX2	1/14 (7)*	13/14 (93)
HepPar-1	1/6 (17)&	5/6 (83)
Chromogranin	1/27 (4)*	26/27 (96)
Synaptophysin	1/27 (4)*	26/27 (96)
Chymotrypsin	0/24 (0)	24/24 (100)
Trypsin	0/26 (0)	26/26 (100)
<b>Molecular Markers</b>		
$\beta$ -Catenin	14/15 (93) – membranous	1/15 (7) – nuclear
E-Cadherin	16/16 (100) – membranous	0/16 (0) – nuclear
p16	4/12 (33)	8/12 (67)
Nuclear p53 accumulation	4/15 (27)	11/15 (73)
SMAD4	16/16 (100)	0/16 (0)

&amp; Focal (10–25% of cells) labeling

\* Only rare, scattered cells