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Intra-ampullary Papillary-Tubular Neoplasm (IAPN): Characterization of Tumoral Intraepithelial Neoplasia Occurring Within the Ampulla:

A Clinicopathologic Analysis of 82 Cases

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Abstract

Background—There has been no uniform terminology for systematic analysis of mass-forming preinvasive neoplasms (which we term tumoral intraepithelial neoplasia) that occur specifically within the ampulla. Here, we provide a detailed analysis of these neoplasms, which we propose to refer to as intra-ampullary papillary-tubular neoplasm (IAPN).

Materials and Methods—Three hundred and seventeen glandular neoplasms involving the ampulla were identified through a review of 1469 pancreatoduodenectomies and 11 ampullectomies. Eighty-two neoplasms characterized by substantial preinvasive exophytic component that grew almost exclusively (>75%) within the ampulla (in the ampullary channel or intraampullary portions of the very distal segments of the common bile duct or pancreatic duct) were analyzed.

Results—(1) Clinical: The mean age was 64 years, male/female ratio was 2.4, and mean tumor size was 2.7 cm. (2) Pathology: The tumors had a mixture of both papillary and tubular growth (each constituting at least 25% of the lesion) in 57%; predominantly (>75%) papillary in 23%, and predominantly (>75%) tubular in 20%. High-grade dysplasia was present in 94% of cases, of which 39% showed focal (<25% of the lesion), 28% showed substantial (25% to 75%), and 27%

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showed extensive (>75%) high-grade dysplasia. In terms of cell-lineage morphology, 45% had a mixture of patterns. However, when evaluated with a forced-binary approach as intestinal (INT) versus gastric/pancreatobiliary (GPB) based on the predominant pattern, 74% were classified as INT and 26% as GPB. (3) Immunohistochemistry: Percent sensitivity/specificity of cell-lineage markers were, for INT phenotype: MUC2 85/78 and CDX2 94/61; and for GPB: MUC1 89/79, MUC5AC 95/69, and MUC6 83/76, respectively. Cytokeratin 7 and 20 were coexpressed in more than half. (4) Invasive carcinoma: In 64 cases (78%), there was an associated invasive carcinoma. Size of the tumor and amount of dysplasia correlated with the incidence of invasion. Invasive carcinoma was of INT-type in 58% and of pancreatobiliary-type in 42%. Cell lineage in the invasive component was the same as that of the preinvasive component in 84%. All discrepant cases were pancreatobiliary-type invasions, which occurred in INT-type preinvasive lesions. (5) Outcome: The overall survival of invasive cases were significantly worse than that of noninvasive ones (57% vs. 93%; $P = 0.01$); and 3 years, 69% versus 100% ($P = 0.08$); and 5 years, 45% versus 100% ($P = 0.07$), respectively. When compared with 166 conventional invasive carcinomas of the ampullary region, invasive IAPNs had significantly better prognosis with a mean survival of 51 versus 31 months ($P < 0.001$) and the 3-year survival of 69% versus 44% ($P < 0.01$).

Conclusions—Tumoral intraepithelial neoplasia occurring within the ampulla are highly analogous to pancreatic or biliary intraductal papillary and tubular neoplasms as evidenced by their papillary and/or tubular growth, variable cell lineage, and spectrum of dysplastic change (adenoma-carcinoma sequence), and thus we propose to refer to these as IAPN. IAPNs are biologically indolent; noninvasive examples show an excellent prognosis, whereas those with invasion exhibit a malignant but nevertheless significantly better prognosis than typical invasive ampullary carcinomas unaccompanied by IAPNs. Twenty eight percent (64 of 230) of invasive carcinomas within the ampulla arise in association with IAPNs.

Keywords

ampulla; ampullary; intra-ampullary; papillary; tubular; tumoral intraepithelial neoplasia

In the past decade, there have been major developments in classification of and terminology for preinvasive neoplasms of the pancreatic ductal system and biliary tract. It is now well established that mass-forming preinvasive neoplasms (which we regard as tumoral intraepithelial neoplasms) in these regions constitute a distinct group that is distinctly different from both conventional adenocarcinomas (for which they are often mistaken because of their tumoral nature), and from “flat” (ordinary) dysplasias, with which they share their “preinvasive” (precursor) nature.^{3-6,8-10,14,22,25-26,29,40,48,53,59}

In the pancreas, intraductal papillary mucinous neoplasm (IPMN) has been widely accepted as a unifying category^{25,26,29,52} embracing a spectrum ranging from very innocuous-appearing lesions lined by gastric-type epithelium (previously referred to as “hyperplasia” in the Japanese literature) to those indistinguishable from colonic villous adenomas, and finally to those that are extensively invasive [previously classified by the World Health Organization (WHO) as “papillary-mucinous carcinoma”].³³ More recently, nonmucinous examples of tumoral intraepithelial neoplasia occurring in this region have also been characterized, namely intraductal tubulopapillary neoplasms (ITPNs; originally referred to as intraductal tubular neoplasms),^{31,55,56,64} which will also be recognized in the new WHO classification as a separate category.

Recognition of pancreatic IPMNs has led to the reappraisal of preinvasive lesions occurring in the biliary tract,^{2,3,29,69} and many authors have adopted the terminology established in the pancreas and begun to classify such lesions of the biliary tract as “biliary IPMN,” a category that encompasses tubular, papillary, and villous preinvasive neoplasms including papillomatosis.^{2,3,28,32,38,46,53,54,68-71} However, some authors object to the term IPMN for

this unification, citing differences in the morphologic repertoire of biliary versus pancreatic IPMNs, in particular, the reduced mucin production of the former.^{32,39,69} Thus, biliary tract counterparts of these lesions (both extrahepatic and intrahepatic) are now being unified under intraductal papillary neoplasm (IPN) for both intrahepatic and extrahepatic lesions.¹

Meanwhile, the intra-ampullary counterpart of these lesions remains poorly characterized. Although duodenal adenomas, which can also involve the papilla of Vater (ie, the duodenal surface of the ampulla) have been fairly well-documented, as have virtually all intestinal (INT)-type adenomas (sporadic or related to familial adenomatous polyposis),^{12,13,18,24,44,45,50} the data on those that arise specifically within the ampulla have been very limited. Such cases have thus far been analyzed either as a part of studies on duodenal (surface) adenomas, or those on conventional cancers of the ampulla.^{11,24,57,63} In the upcoming WHO blue book, those that resemble INT adenomas will continue to be classified as INT adenomas, along with the adenomas of duodenal surface, whereas those with pancreatobiliary (PB) phenotype will now be recognized under a separate name (separate category) as “noninvasive PB-type neoplasms.”

Here, we document the morphologic spectrum, immunophenotypic features, and clinical characteristics of 82 preinvasive mass-forming intra-ampullary neoplasms and their associated invasive carcinomas. We provisionally propose the descriptive term intra-ampullary papillary-tubular neoplasm (IAPN) for this group until their nature and kinship to other preinvasive neoplasms occurring in this region are further elucidated.

MATERIALS AND METHODS

These studies were conducted in accordance with institutional review board requirements.

Case Selection

From the authors' institutional and consultation files, 1480 ampullary resections (1469 pancreatoduodenectomies and 11 ampullectomies) were reviewed. Among 317 cases of carcinomas originally classified as ampullary, 69 were reclassified as secondary involvement of the ampulla and excluded. Of the remaining 248 primary ampullary tumors, 82 were found to be mass-forming (grossly recognizable) neoplasms that were preinvasive and grew almost exclusively (>75%) within the ampullary channel [presumably they arose from the epithelium of the common channel and/or the very distal segments of the pancreatic duct or common bile duct (CBD)]. Mucin hypersecretion was not considered as a criterion for inclusion. Presence or extent of invasive carcinoma was disregarded in case selection as had been carried out in the classification of similar lesions, namely pancreatic IPMNs, ITPNs, and biliary IPNs.^{4,26}

For the summary definition, see the summary text (Textbox 1).

Excluded accordingly with a purist's approach were:

1. Similar neoplasms originating in the duodenal surface of the papilla of Vater: Cases in which the preinvasive neoplasm showed more than negligible involvement of the duodenal surface of the papilla of Vater were excluded. To clearly distinguish intra-ampullary lesions from INT adenomas, which sometimes involve the ampulla and extend in a pagetoid fashion into the ampullary channel/distal ducts, an arbitrary requirement that greater than 75% of the preinvasive lesion be located within the ampulla was used.
2. Similar neoplasms occurring in the ducts: Only the cases with neoplasms occurring in the very distal (intra-ampullary) segments of the CBD or pancreatic ducts were

included. Cases in which the preinvasive neoplasm showed more than negligible involvement of the more proximal components of the CBD or pancreatic ducts were excluded. The arbitrary requirement that greater than 75% of the preinvasive lesion be located within the ampulla was used with these cases as well.

3. Exuberant examples of flat intraepithelial neoplasia: Flat-type dysplastic lesions may in some instances exhibit taller papillary configuration. Such lesions were excluded unless they formed grossly detectable lesions or compact tumorous nodules distinct from the adjacent mucosa.
4. Colonization (cancerization of surface mucosa): Invasive carcinomas that colonize the surface epithelium (“cancerization”), and on occasion, showed exophytic growth toward the lumen, were excluded.

Demographic and Clinical Data

Information regarding the patients’ age, sex, and clinical outcome were obtained from the patient’s charts, by contacting the primary physicians, or through the Surveillance and Epidemiology End Results database.

Histomorphologic Analysis

Growth Pattern—Growth patterns in the preinvasive lesions were evaluated for the amount of papillary or tubular growth. The tumors were classified as “papillary” if greater than 75% of the growth pattern was papillary (or villous); as “tubular” if greater than 75% was tubular; and as “tubulopapillary” if a secondary pattern constituted greater than 25% of the preinvasive lesion.

Dysplasia—Presence of high-grade dysplasia (HGD), based on the criteria applied in pancreatic IPMNs and biliary IPNs,^{1,4,8-10,25,29,48,53,59} was recorded and its extent scored as “focal” if it was identified in less than 25% of the lesion; as “substantial” if it was greater than 25% to less than 75% of the lesion; and as “extensive” if it occupied greater than 75% of the lesion.

Cell-Lineage Morphology—Cell-lineage morphology determination was made based on a modification of the histomorphologic criteria established for pancreatic IPMNs.^{8,22} Accordingly, the lesions were classified as INT if the lesion resembled colonic villous adenomas (or INT-type IPMNs) or alternatively as gastric/pancreatobiliary (GPB)-type if it was similar to either the gastric or PB-type IPMNs. Gastric and PB lineages were grouped together in accordance with recent concepts in pancreatic histology which favor the combined classification of these 2 lineages because of their close association, shared immunophenotype, and common co-occurrence.^{8,22}

Cell-lineage morphology was analyzed by 2 different approaches: (1) the existence of any lineage was acknowledged regardless of the amount, even if it was a minimal percentage of the lesion or incompletely developed; (2) with a forced-binary approach resulting in a case assignment of either the INT or GPB category (without benefit of a third alternative) based on the predominant phenotype.

Budding—Tumor budding was defined as the presence of ≥ 5 isolated single cancer cells or clusters composed of fewer than 5 cancer cells in the stroma of the invasive front per field measuring 0.785 mm² using a 20 $\times$ objective lens. The extent of the budding was then further classified as “high” if there were ≥ 3 budding foci and as “low” if there were less than 3 budding foci or no budding focus.

Immunohistochemical Analysis

Cell-Lineage Markers—Immunohistochemical analysis was performed for cell-lineage markers known to be differentially expressed in different components of the gastrointestinal tract, and which have also been used for subclassification of pancreatic and biliary IPNs.

- MUC1 (mammary gland type of apomucin) has been shown to be a fairly sensitive marker of PB differentiation, and is expressed in most of invasive ductal adenocarcinomas of PB origin, as well as in the PB-type of IPMN, but is fairly uncommon in INT-type adenocarcinomas or INT-type IPMN.^{6,8,15,22,35,64-67}
- MUC2 (apomucin of INT goblet-cell type) has been shown to be a fairly specific marker of INT differentiation. Among pancreatic and biliary intraductal papillary/tubular neoplasms, diffuse/strong expression of MUC2 is mostly confined to the INT subtype, and is otherwise seldom seen in other types such as GPB (except in scattered goblet cells which can occur in any tumor type). Among invasive carcinomas, its expression is mostly limited to the mucinous type of invasive carcinomas.^{7,8,15,34,35,58,66,67}
- CDX2 (intestinal transcription factor), an upstream regulator of MUC2, has been shown to be another reliable marker of INT differentiation, with an expression profile closely paralleling that of MUC2.^{8,15,36,41,61,62}
- MUC5AC (apomucin of the gastric foveolar cell type) has been regarded as a marker of gastric-foveolar differentiation. Although MUC5AC is not constitutively expressed in normal PB epithelium, it is widely detected in a variety of pancreatic and biliary neoplasms, including IPMNs of any subtype (not only gastric-type but also others) and a substantial percentage of invasive PB-type adenocarcinomas.^{15,27,34,37,42,55} INT-type adeno-carcinomas, however, generally test negative for this marker.³⁶
- MUC6 (apomucin of the gastric pyloric cell type) has been shown to be expressed in gastric pyloric, gastric cardiac, and duodenal Brunner glands. The expression of MUC6 is commonly observed in neoplasms or their components with a pyloric gland appearance, such as basilar glandular elements of IPMN and mucinous cystic neoplasms, as well as the so-called “pyloricgland-type adenomas,” which are viewed as part of the gastric-type IPMN lineage.^{15,16,37}
- Cytokeratin (CK)7 (a subtype of high molecular weight CKs) has been shown to be expressed widely in PB ductal epithelium and its neoplasms, including PB-type IPMNs and ductal adenocarcinomas, but not much in INT epithelium and its neoplasms.^{17,21,23,27,34,49,60}
- CK20 (a subtype of low molecular weight CKs) has been shown to be expressed in INT-type epithelium, INT-type adenocarcinomas, and intensely expressed in INT-type IPMNs.^{17,19,21,23,27,49,60}

Methodology—Immunohistochemistry was performed using a polymer-based detection system (EnVision+; Dako, Carpinteria, CA) with mouse monoclonal antibodies according to the manufacturer’s instructions. Sections were deparaffinized and rehydrated with deionized water. Then, they were heated in citrate buffer, pH 6.0, using an electric pressure cooker for 3 minutes at 12 to 15 pounds per square inch at approximately 120°C and cooled for 10 minutes before immunostaining. All slides were loaded onto an automated system (Autostainer; Dako) and exposed to 3% hydrogen peroxide for 5 minutes, incubated with primary antibody for 30 minutes, incubated with labeled polymer (EnVision+dual link) for 30 minutes, incubated in 3’3-diaminobenzidine as a chromogen for 5 minutes, and counterstained with hematoxylin for 5 minutes. These incubations were performed at room

temperature. Between incubations, sections were washed with tris-buffered saline. Coverslipping was performed using the Tissue-Tek SCA coverslipper (Sakura Finetek USA, Inc, Torrance, CA). The negative (for which the primary antibody was replaced by tris-buffered saline) and positive controls were processed with the other slides in the study. The detailed specifications of the antibodies are provided in Table 1.

Evaluation of Immunohistochemistry—The percent of cells showing membranous (MUC1), cytoplasmic (MUC2, MUC5AC, MUC6, CK7, and CK20), and nuclear (CDX2) labeling were recorded. As is customary in most studies, labeling in less than 10% of the cells was designated as “negligible/negative” expression. Labeling in 10% to 50% of tumor cells was regarded as “focal positive,” whereas greater than 50% was considered “diffuse positive.”

Statistical Analysis—Patient and tumor characteristics were analyzed by an unpaired Student *t* test or χ^2 tests. Overall survival was analyzed using the Kaplan-Meier method and differences among groups were assessed by log-rank test. A Cox proportional hazard regression (version 2.9.1; open source statistical software) was used to identify independent factors associated with postresection survival. All tests were 2-sided, and statistical significance was defined as *P* value less than 0.05.

RESULTS

General Characteristics

Eighty-two cases fulfilled the criteria described for IAPN (Textbox 1). The prevalence among ampullary glandular neoplasms was 33% and 5.5% among pancreatoduodenal/ampullary resection specimens. The mean age was 64 years (range: 27 to 85 y). Fifty-seven patients were male and 24 were female (ratio: 2.4). Main presentation symptoms were available in 19 cases and included jaundice (19), weight loss (4), abdominal pain (4), nausea/vomiting (3), pruritis (2), and dark urine/light stool (2), and tarry stool (1). Imaging studies (5 endoscopic retrograde cholangiopancreatography, 9 computed tomography, and 1 magnetic resonance imaging) generally described dilated CBD and intra/extrahepatic ducts, ampullary, duodenal or pancreatic mass, and enlarged and/or irregular papillae. The preoperative diagnosis was available for 49 cases and was “ampullary mass” in 18 cases, “ampullary carcinoma” in 20, “duodenal carcinoma” in 4, “distal CBD carcinoma” in 3, “pancreatic carcinoma” in 1, and “pancreatic mass” in 3 cases (Table 2).

Macroscopic Findings

These tumors were characterized by prominent exophytic growth within dilated intra-ampullary ducts and formation of obstructive papillary/polypoid masses, often with dilatation of the upstream biliary or pancreatic ducts (Fig. 1). The macroscopic pattern mostly corresponded to what has been referred to as an “intramural protruding form,”^{57,63} although in rare cases there was minimal involvement of the duodenal surface of the papilla of Vater, thus representing the “exposed protruding form” or “ulcerating form.” By definition, those cases with more prominent involvement of the papilla were excluded. Mucin hypersecretion was recognized in 7 cases (8.5%). The mean overall tumor size was 2.7 cm (range: 0.8 to 6.7 cm). Although 2 preinvasive tumors were less than 1 cm (0.8 and 0.9 cm), they were included in this study because they were easily distinguished from the flat lesions by their compact exophytic growth (Fig. 1) and their clear-cut delineation from the surrounding tissue.

Microscopic Findings

These lesions were characterized by well-organized, back to back epithelial units, either in tubular (Fig. 2A) or papillary (Fig. 2B) architecture or both, with minimal or no intervening stroma between the units, similar to other preinvasive neoplasms. The base of the lesions was sharply demarcated; however, the dysplastic process often showed complexity because of the involvement of the tributary glands comprising the ampullary ductules. This created an architectural complexity and a pseudoinvasive pattern, which, at times, was difficult to distinguish from true invasion. In 38 cases (46%), the exophytic (preinvasive) lesion extended by pagetoid spread to the duodenal surface of the papilla of Vater, but by definition this duodenal lumen-facing component comprised less than 25% of the tumor.

Histologic Growth Pattern

Forty-seven cases (57%) had a tubulopapillary configuration (each component was >25% of the lesion), (Tables 2, 3), whereas 19 (23%) were predominantly (>75%) papillary (or villous), and 16 (20%) were predominantly tubular. The mean tumor size did not seem to differ between these groups: 2.4 cm in the papillary and tubular groups and 2.9 cm in the tubulopapillary group (Table 3).

Papillary examples had a higher tendency for HGD than the tubular and tubulopapillary groups ($P<0.05$). The extent of HGD in the papillary group was focal in 11%, substantial in 37%, and extensive in 47% of cases; these figures were 49%, 26%, and 19% for tubulopapillary, and 44%, 25%, and 25% for tubular examples. However, the prevalence of an associated invasive carcinoma was lower in the papillary group (68%) than in tubulopapillary (81%) or tubular (81%) groups. There were no significant differences in prognostic factors such as tumor stage, lymph node involvement, or 3 and 5-year survival rates between these groups.

Dysplasia

Five cases (6%) had no HGD, 32 (39%) had focal, 23 (28%) had substantial, and 22 cases (27%) had extensive HGD (Fig. 3). The prevalence of an associated invasive carcinoma for these groups was 0%, 76%, 87%, and 86%. In addition, the 3 and 5-year survival rates of the former 2 groups (focal or no HGD) seemed to be higher than those of the latter 2 groups (substantial or extensive HGD), but the difference was not statistically significant ($P = 0.09$) (Table 4).

Histomorphologic Subtyping Based on Cell Lineage

Using an approach that acknowledged any existing pattern of cell-lineage morphology, almost half of the cases (37 cases; 45%) were found to have mixed patterns (at least some foci of a secondary pattern, Fig. 4), whereas 35 (43%) were pure INT (Fig. 5) and 10 cases were (12%) pure GPB (Fig. 6). When evaluated with the forced binary classification approach, the predominant pattern was INT (Fig. 5) in 61 cases (74%) and GPB (Fig. 6) in 21 cases (26%) (Table 5).

On the basis of the combination of predominate cell-lineage morphology and growth pattern, the cases were classified into the following categories:

INT-type (61 Cases)—The majority of INT-type cases were similar to conventional colonic/duodenal tubular adenomas consisting of relatively simple villous or tubular glandular units, lined by tall columnar INT-type cells with pseudostratified cigar-shaped nuclei (Fig. 4A). Occasionally, cribriform architecture was observed. The apical cytoplasm was usually densely chromophilic, but was pale or clear with abundant apical mucin in 3

cases. Goblet, brush border, and/or Paneth cells were prominent in some cases (Fig. 5B). Mucin hyperproduction into the lumen, akin to that seen in pancreatic IPMNs, was seen in only 3 cases.

Forty (66%) of the INT-type cases were tubulopapillary, 14 (23%) were tubular, and 7 (11%) were papillary (or villous). Importantly, 43% had secondary GPB cells (Fig. 4), which is unusual in conventional colonic/duodenal adenomas. Prevalence and proportion of HGD in the INT group was significantly lower than that of the GPB group presented below. Seven percent of cases had no HGD and 52% had focal, whereas 30% had substantial, and only 11% of cases had extensive HGD. An associated invasive carcinoma was identified in 77% of INT cases. The type of invasive carcinoma was INT in 79% and GPB in 21% of these cases; the size of invasion was less than 0.5 cm in 13%, 0.5 to 1 cm in 30%, and greater than 1 cm in 57% of cases.

GPB-type (21 Cases)—Two distinct subtypes of GPB could be discerned based on cytoarchitectural characteristics. The first was characterized by a papillary (75%) or tubulopapillary (25%) growth pattern and cytomorphology similar to that of PB-type IPMNs (Fig. 6A). The second GPB subtype was characterized by a striking tubular growth pattern and an overall appearance of a pyloric gland adenoma (Fig. 6B).

PB-papillary subtype (16 cases): Almost all PB-papillary-type cases had complex arborizing papillae. The cytologic features often showed transition to a more gastric phenotype (Fig. 6A), which further supported their kinship with the gastric type and also justified their combined classification. However, all had HGD/carcinoma in situ in the papillary areas. In addition, HGD was extensive in 75% and substantial in the remaining 25%; none of the cases were classified as focal. An associated invasive carcinoma was identified in 81% of PB-papillary-type cases all of which were GPB-type, and tended to be larger (0% were <0.5 cm, 38% were 0.5 to 1 cm, and 62% >1 cm) than invasions seen in INT-type or the gastric-tubular type discussed below.

Gastric-tubular subtype (5 cases): The gastric-tubular-type lesion was recognized as a separate variant because of its highly distinctive morphology among lesions with GPB lineage. The lesions were characterized by a closely packed, uniform, tubular growth pattern reminiscent of pyloric or Brunner glands. The glands were arranged back-to-back and lined by a single layer of cuboidal to columnar GPB-type cells with basally oriented nuclei and abundant apical mucinous cytoplasm (Fig. 6B). Two gastric-tubular-type cases formed polypoid masses resembling the pyloric gland type of adenoma in that one was devoid of HGD and the other exhibited transformation into arborized papillary areas with HGD. The remaining 3 cases showed monotonous, small tubular proliferation with extensive HGD and formation of expansile masses which resembled intraductal tubular/tubulopapillary carcinoma of the pancreas, although some with a more mucinous-appearing cytoplasm. Expansile proliferation replaced most of the residual ductal epithelium and made recognition of the intraductal (duct-confined) nature of the process challenging. An associated invasive carcinoma was present in 4 cases (80%) and all were of PB-type. Invasion, however, seemed to be relatively small at the time of diagnosis, compared with INT-type or PB-papillary subtype, in that 3 (75%) were 0.5 to 1.0 cm, and only 1 (25%) was larger than 1 cm.

No significant difference in prognostic factors such as pathologic tumor (pT) stage, lymph node involvement, or 3 and 5-year survival rates were identified among these subtypes.

Cases With an Associated Invasive Carcinoma (64 Cases)

Sixty-four of 82 cases (78%) had an associated invasive carcinoma (64 of 230, 28%, of all invasive carcinomas within the ampulla arose in association with IAPNs). The average age

and sex ratio of the patients was similar in the invasive and noninvasive groups (64 vs. 63 y; the male/female ratio was 2.2 vs. 3.5, $P = 0.91$ and $P = 0.44$, respectively). The overall size of the tumor tended to be larger in the invasive group than in the noninvasive (2.8 vs. 2.1 cm, respectively; $P = 0.04$). The size of invasion was less than 0.5 cm in 6 cases (9%), 0.5 to 1 cm in 22 (34%), and greater than 1 cm in 36 cases (56%).

The histologic type of invasive carcinoma included 60 ordinary adenocarcinomas and 4 mixed adenocarcinomas (2 with mucinous, 1 squamous, and 1 with neuroendocrine components).

As for the cell-lineage morphology, associated invasive carcinomas were classified as pure INT-type in 5 cases (8%), mixed in 46 (72%), and pure PB-type in 13 cases (20%). On the basis of the forced-binary approach (which eliminated the mixed category), however, the cases were finally divided into INT-type (37 cases; 58%) and PB-type (27 cases; 42%). The representative histology of each type is shown in Figure 7.

In terms of preinvasive components, among the 61 preinvasive lesions of INT cell lineage, 47 (77%) had an associated invasive carcinoma including 37 invasive lesions of INT cell lineage and 10 invasive lesions of PB cell lineage. On the other hand, among the 21 preinvasive lesions of GPB cell lineage, 17 (81%) had an associated invasive carcinoma all of which were of PB cell lineage (Table 5).

Among the 64 cases with an associated invasive carcinoma, the preinvasive component was INT-type in 47 (73%) and GPB-type in 17 cases (27%). There was lineage concordance between preinvasive and invasive components in 54 cases, whereas 10 were discordant; all 10 discordant cases had INT-type preinvasive neoplasms but PB-type invasion. All cases with a GPB-type preinvasive component also had a PB-type invasive component.

Immunophenotypic Features

Preinvasive Components—Fifty-nine cases were available for immunohistochemical staining. The preinvasive components of INT cell-lineage morphology (41 cases) showed immunolabeling (diffuse+focal) for MUC2 (31%+54%) in 85% of the cases, 94% (78%+16%) for CDX2, 93% (83%+10%) for CK20, 21% (8%+13%) for MUC1, 31% (5%+26%) for MUC5AC, 24% (3%+21%) for MUC6, and 63% of cases (53%+10%) for CK7 (Figs. 8, 9A).

Those with GPB cell-lineage morphology (18 cases) showed immunolabeling (diffuse+focal) for MUC2 in 22% (0%+22%) of the cases, 39% (11%+28%) for CDX2, 39% (28%+11%) for CK20, 89% (67%+22%) for MUC1, 95% (56%+39%) for MUC5AC, 83% (39%+44%) for MUC6, and 89% (89%+0%) of cases showed immunolabeling for CK7 (Figs. 8, 9B).

The sensitivity and specificity for INT cell-lineage markers were as follows: MUC2, 85% and 78%; CDX2, 94% and 61%; and CK20, 93% and 61%. The sensitivity and specificity for GPB cell-lineage markers were as follows: MUC1, 89% and 79%; MUC5AC, 95% and 69%; and MUC6, 83% and 76%. CKs 7 and 20 were coexpressed in 53% of all cases available for immunohistochemical staining.

When the subsets of GPB type were analyzed separately, it was noted that all PB-papillary cases had at least focal MUC5AC, and all gastric-tubular subtype had at least focal expression of MUC1.

Invasive Components—Tissue from 24 invasive INT-type carcinomas was available for evaluation. Immunolabeling (diffuse+focal) was positive for the following percentage of cases: MUC2 67% (25%+42%); CDX2 78% (52%+26%); CK20 83% (75%+8%); MUC1 46% (4%+42%); MUC5AC 59% (13%+46%); MUC6 17% (4%+13%); and CK7 67% (54%+13%).

Twenty-three PB-type invasive carcinomas were available for evaluation. Immunolabeling (diffuse+focal) was positive for the following percentage of cases: MUC2 17% (4%+13%); CDX2 34% (17%+17%); CK20 48% (35%+13%); MUC1 96% (83%+13%); MUC5AC 61% (26%+35%); MUC6 39% (22%+17%); and CK7 83% (83%+0%).

For invasive carcinoma of the INT cell lineage, sensitivity and specificity results were as follows: MUC2 67% and 83%; CDX2 78% and 66%; and CK20 83% and 52%. Sensitivity and specificity for invasive carcinoma of the PB cell lineage were as follows: MUC1 96% and 54%; MUC5AC 61% and 41%; MUC6 39% and 83%; and CK7 83% and 33%.

Prognosis (Clinical Outcome)

Prognostic Stratifiers—Cases without invasion had a very good prognosis, as evidenced by 3 and 5-year survival rates (100% and 100%) significantly better than those cases with an associated invasive carcinoma (69% and 45%, respectively) (Table 2). There were significant differences between these 2 groups in terms of tumor size (2.1 vs. 2.8 cm), and HGD proportion (no or focal HGD/substantial or extensive HGD 67%/33%, $P = 0.04$ vs. 39%/61%, $P = 0.04$). Only 1 patient with noninvasive carcinoma died; he had substantial HGD/carcinoma in situ and died 85 months after undergoing a Whipple resection.

Univariate and multivariate analyses were performed on 53 cases with an associated invasive carcinoma for which all the parameters tested were available (eg, cases with incomplete lymph node dissection because of local excision, like ampullectomies, were excluded). In univariate analysis, pT stage ($P < 0.01$), lymph node involvement ($P = 0.01$), and tumor budding ($P = 0.03$) were found to be the significant prognostic factors, whereas venous invasion ($P = 0.06$) and pattern of invasion (infiltrative vs. expansile) also approached statistical significance ($P = 0.08$) (Table 6). In a stepwise, multivariable Cox regression analysis which incorporated these 5 factors, pT stage ($P = 0.01$) was the only significant independent factor related to prognosis, although tumor budding did approach statistical significance ($P = 0.09$) (Table 7).

Comparison With Other Ampullary Carcinomas

When IAPNs with an associated invasive carcinoma were compared with conventional invasive carcinomas of the ampulla, the mean tumor size was not significantly different (2.8 cm vs. 2.5 cm), but there was a significant difference in the size of invasion (mean size of invasion 1.4 cm vs. 1.9 cm, $P < 0.001$). Minimal invasion (< 5 mm) was more common in the former (9% vs. 2%). IAPNs with an associated invasive carcinoma also had significantly better tumor differentiation ($P < 0.001$), were more frequently of INT cell lineage ($P < 0.001$), had a lower tumor stage ($P < 0.001$), and had less lymph node involvement ($P = 0.05$). More importantly, cases of invasion associated with IAPNs had a significantly better prognosis than conventional invasive carcinomas of the ampulla. The mean survival time was 51 versus 31 months ($P < 0.001$) and the 3-year survival rate was 69% versus 44% ($P < 0.01$); although, the difference in 5-year survival rate (45% vs. 28%) did not reach statistical significance ($P = 0.06$) (Table 8, Fig. 10).

DISCUSSION

Definition and Delineation From Similar Neoplasms

The tumor-forming intraepithelial neoplasms analyzed in this study are remarkably analogous to IPMNs and ITPNs of the pancreas and to biliary IPNs.^{2,3,25,26,29,64,69} Their striking similarities with these neoplasms warrant their classification in a parallel category. As with their counterparts in the neighboring sites, these neoplasms are characterized by exophytic (papillary and/or polypoid/tubular) growth, variable cellular lineage (INT or GBP), and a spectrum of dysplastic change (adenoma-carcinoma sequence). Until now, they have been classified as conventional adenocarcinomas of the ampulla, or included in studies on “adenomas” of the duodenum, which may involve the duodenal surface of the papilla of Vater, and classified as ampullary. However, it is clear that they must be distinguished from the former, because, as is now widely accepted, invasive carcinomas arising in association with mass-forming preinvasive neoplasms (eg, invasive carcinomas in IPMNs) have distinctive characteristics, including different biology and clinical behavior. These neoplasms also ought to be delineated from the conventional INT-type duodenal adenomas that involve the duodenal surface at the Vaterian region. Although there are various similarities between these entities, it is necessary to classify the intra-ampullary ones separately as is carried out for the mass-forming preinvasive neoplasms in the PB tract, which are classified based on their specific site of origin, and furthermore, it is safe to assume that the internal aspect of the ampulla (a transitional region with various distinctive histomorphologic characteristics) confers specific properties to the tumors. Indeed, in this study, these neoplasms were found to have various site-specific characteristics, as discussed below.

Terminology

Herein, we provisionally propose to designate these neoplasms as “intra-ampullary papillary-tubular neoplasm.” The term “intra-ampullary” is proposed to indicate both the localized and preinvasive nature of these neoplasms. Their exophytic (mass-forming) nature, in contrast, is highlighted by the name “papillarytubular,” which emphasizes the fact that these tumors can have either papillary or tubular or both configurations, in a mixture. The name papillary-tubular is favored over tubulopapillary (or “tubulovillous”), because, the latter (1) is a term that has been specific to mixed-type neoplasms in the gastrointestinal tract, whereas, with IAPNs, the mixed type is common but some cases are purely papillary or purely tubular; (2) may give the impression that these neoplasms are more commonly tubular than papillary, but in fact the papillary pattern is more common; and (3) is now a term used in the category designation for a specific pancreatic tumor type, namely ITPNs²⁶ (a designation also advocated in the upcoming WHO classification). Only a small percentage of IAPNs display the features of pancreatic ITPNs. Finally, the possibility of incorporating the word “mucinous” in the category designation was considered but dismissed, because, this descriptor was recently dropped from the nomenclature of biliary neoplasms because of the fact that, like IAPNs, they often produce only minimal mucin. This is in contrast with pancreatic IPMNs, which are often characterized by profuse mucin production.

Incidence

IAPNs are relatively rare. They constitute 33% (82 of 248 cases) of primary ampullary tumors and 5.5% (82 of 1480 cases) of pancreatoduodenectomies/ampullectomies with neoplasm. The frequency of a preinvasive component in ampullary cancers is highly variable in the literature, presumably because of marked definitional differences. In some studies, it was reported to be up to 90%. In this study, one third of the cases with invasive carcinoma in the ampulla were associated with an IAPN component. This percentage is

higher than in the pancreas where IPMNs have been implicated in 2%³⁰ to 10%⁴⁷ of invasive carcinomas, or in the gallbladder where we recently found 10% of invasive cancers to have an associated tumoral intraepithelial neoplasia²⁰ (reportedly 3% to 18% in the literature).

Clinicopathologic Characteristics

The mean age at diagnosis, 64 years, is similar to that of patients with other cancers of the ampullopacreatobiliary region.³⁰ As in conventional carcinomas of the ampullary region, they occur predominantly in males (male/female ratio: 2.4 vs. 1.3). The mean tumor size is also similar to that of the resected carcinomas seen in pancreatoduodenectomies: 2.8 cm (0.8 to 6.7 cm; vs. 3 cm in other carcinomas). Not surprisingly, the patients often present with jaundice.

Macroscopically, most IAPNs, by definition, have minimal exophytic growth at the duodenal surface aspect of the papilla of Vater. However, they sometimes form a mucosal protuberance in the duodenal lumen because of the underlying proliferative process, which fills the intraampullary/ductal lumen. The duodenal orifice of the ampulla is often wide, irregular, and occasionally ulcerated. On cut sections of ampulla, IAPNs are characterized by polypoid or papillary (granular-exophytic) lesions, which fill the ampullary channel (or the intra-ampullary tips of both the CBD and pancreatic duct).

Microscopically, there is a variable degree of papillary and tubular configuration. About a quarter of the lesions are predominantly (>75%) composed of papillary elements, another quarter are tubular; however, more than half of the cases exhibit a substantial mixture of the 2 growth patterns (ie, tubulopapillary). The frequency of the mixed pattern may partially be attributable to the complexity of the ampullary mucosa, which contains numerous tributary glands, which impart a tubular architecture to the process when involved by the pagetoid spread of IAPN cells. The significance of the growth patterns needs further analysis, because the incidence and amount of HGD tended to be higher in those cases with papillary configuration although did not otherwise seem to have statistically significant correlation with either incidence of invasion or overall prognosis.

IAPNs display a spectrum of dysplasia (neoplastic transformation) not only within the entity, but also commonly within a given patient. More than 80% of the cases exhibit a mixture of low and high-grade dysplastic foci within the same lesion. The overall incidence of HGD is very high; only a small minority (6%) of cases is entirely devoid of HGD. In about one third of the cases, HGD is focal, in another third, substantial (25% to 50% of the lesion), and yet, in about a quarter, it is extensive. The existence and amount of HGD seem to trend toward higher incidence of invasive carcinoma and more aggressive behavior; however, this association did not reach statistical significance in this study. Of note, all 5 cases, which lacked HGD also lacked invasive carcinoma. This very high incidence of HGD is intriguing especially considering the relatively early stage detection of these lesions. This suggests that once the neoplastic transformation begins in the ampullary epithelium, it progresses rather rapidly. This may be attributable to either some inherent vulnerability of this mucosa or its ready exposure to different milieu with its potential instigators including pancreatic secretions, bile, and duodenal secretions.

Like their counterparts in the pancreatic and biliary tract, IAPNs exhibit a spectrum of cell lineages that recapitulate those found in different compartments of the gastrointestinal tract. Interestingly, in about half of the cases, a mixture of these cell lineages is seen in coexistence, which may not be surprising considering the transitional nature of the ampulla. This high incidence of mixed lineage also distinguishes IAPNs from the conventional INT-

type adenomas that occur at the duodenal surface of the papilla of Vater, which are uniformly of INT-type and often show different molecular events.⁵¹

Although mixed lineage was common when neoplasms were evaluated using a purist's approach, when a forced-binary approach based on the predominant pattern was used, the majority (74%) of IAPN cases could be designed INT type (closely resembling pancreatic INT-type IPMNs or colonic adenomas than GPB lesions), whereas the remaining 26% were placed into the GPB category. However, many cases placed into the INT category exhibited subtle, often hybrid features different from ordinary colonic adenomas. The GPB category could be further subdivided into 2 groups (1) those with a prominent papillary configuration resembling PB-type IPMNs, and (2) those which are predominantly tubular with pyloric gland adenoma-type features. Although the prevalence of extensive HGD was fairly low in INT cases (11%), it was fairly common (75%) in PB-papillary cases. The associated invasive carcinoma also tended to be smaller in the INT-type. The gastric tubular-type cases were rare (6%) and more difficult to characterize. Interestingly, 4 of 5 gastric-tubular-type cases in this study had an associated invasive carcinoma but 3 of these were smaller than 1 cm.

Immunohistochemical markers used in IAPNs do not have the same degree of reliability for distinguishing cell lineages as they do, for example, in pancreatic IPMNs.^{8,22,43,53} This is not surprising when the hybrid and transitional nature of the ampulla, as well as the frequency of mixed phenotypes at the histologic level are considered. Even the most reliable marker for INT differentiation in IAPNs, MUC2, was found to have sensitivity and specificity of only 85% and 78%, respectively, whereas CDX2 was more sensitive but entirely lacked specificity (90% and 61%). For the GPB lineage, markers that had some degree of sensitivity and specificity were MUC1 (89% and 79%) and MUC6 (83% and 76%). Moreover, the CK profile was entirely nondiscriminatory, in that, CK7 and CK20 were coexpressed in more than half of the cases. More importantly, CK7, which is regarded as a good marker of GPB differentiation was expressed in a high proportion (63%) of INT cases, and CK20, which is generally considered a good marker of the INT phenotype, was expressed in a substantial number (39%) of GPB. This divergence from the conventional, expected profile can be taken as further evidence of the transitional nature of IAPNs and their pronounced ability to form hybrid phenotypes.

Invasive Carcinomas Associated With IAPNs

IAPNs commonly (78%) have an associated invasive carcinoma at the time of diagnosis. However, in almost half of these, the invasive carcinoma is less than 1 cm. Invasive carcinoma is more prone to develop in larger IAPNs (mean size was 2.8 cm in invasive vs. 2.1 cm in noninvasive cases, $P = 0.04$). All cases that have an associated invasive carcinoma have at least focal HGD. All 5 cases that lacked HGD also lacked an associated invasive carcinoma; however, overall, the amount of HGD does not seem to correlate significantly with invasion. There does not seem to be any association between propensity for invasion and the configuration (papillary vs. tubular) of the preinvasive neoplasm.

Invasive carcinomas that arise in IAPNs are mostly tubule-forming (glandular-type) adenocarcinomas that commonly (72%) show INT/PB hybrid features. This further corroborates the transitional nature of this area and its capacity to form different lineages. However, when a forced-binary classification based on the predominant (favored) pattern was used, 58% of invasive carcinomas in IAPN become classifiable as INT and 42% as PB. The cell lineage of an associated invasive carcinoma often but not always parallels that of the noninvasive component; in 84% (54 of 64), there was a correlation between the 2 components and in 16% (10 of 64), there was a discrepancy. The discrepancy occurred only

in INT-type IAPN, of which 21% (10 of 47) led to PB-type invasive carcinoma. All invasive carcinomas that arose from GBP-type IAPNs were of PB-type.

Biologic Behavior and Clinical Outcome Parameters

The prognosis for IAPNs when both noninvasive and invasive cases are considered, is significantly better than that of other invasive carcinomas of the ampulla, and is incomparably better than pancreatic ductal adenocarcinoma. Not surprisingly, noninvasive examples have a far better prognosis: the 3 and 5-year survival rates are 100%. In this study, the only patient from the noninvasive group who died of disease had extensive HGD and died 8 years after undergoing a pancreatoduodenectomy. The survival rate for patients with invasive IAPN (mean length of survival, 51 months, and the 3-year survival rate, 69%), is not quite as good as the noninvasive cases but is nevertheless still better significantly than that of other invasive carcinomas of the ampulla without an accompanying IAPN component (mean length of survival is 31 months and the 3-year survival rate is 44%; $P < 0.01$), although the difference in survival rate at 5 years (45% vs. 28%) did not reach statistical significance in this study ($P = 0.06$), which raises suspicion that the gap between the 2 may diminish in long-term follow-up. The survival advantage of IAPN-associated cases over non-IAPN associated ones is partly attributable, not surprisingly, to early detection of the invasive component tagged by the noninvasive (IAPN) process, including smaller size of invasion (1.4 vs. 1.9), more early-stage cancers (T1/2: 86% vs. 58%), and lower incidence of lymph node metastasis (24% vs. 42%).

Within the group of invasive IAPNs, the pathologic parameters that correlated with prognosis in univariate analysis and thus are suggested to be included in surgical pathology reports were as follows: stage (pT-stage and N-status), tumor budding, venous invasion, and infiltrative versus expansile growth. Among these, the T-stage seemed to be the only independent prognostic parameter, whereas budding approached the level of independence.

CONCLUSIONS

In conclusion, mass-forming preinvasive neoplasms occurring within the ampulla have many similarities to biliary and pancreatic papillary, intraductal papillarymucinous, and tubulopapillary neoplasms, in that they exhibit a spectrum of dysplastic change, variable configuration, and different cell lineages, often in a mixture. We believe these neoplasms warrant classification under a unified category for which we propose the descriptive name IAPN. IAPNs are indolent, and have a better overall prognosis for invasive examples than other invasive cancers which arose in this region. However, IAPNs associated with invasive carcinoma often have a malignant clinical course, albeit not as aggressive as of those that are unaccompanied by IAPN.

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Definition of Intra-ampullary Papillary-Tubular Neoplasm

A Neoplasm that is:

Preinvasive (dysplastic)

Mass-forming; exophytic (papillary or polypoid)

Compact

Distinct from neighboring mucosa

Localized almost exclusively within the ampulla

Growing predominantly (>75%) within the channel and/or the very distal segments of the pancreatic duct or common bile duct

With only minimal (<25%), if any, involvement of the duodenal aspect of the papilla

And only minimal (<25%), if any, intramucosal extension into the proximal aspects of the common bile duct or pancreatic duct

FIGURE 1.

A, Prominent exophytic growth dilating and filling the intra-ampullary ducts and forming obstructive papillary/ polypoid mass. B, By definition, there is only minimal (<25%) tumor at the duodenal surface of the papilla. CBD indicates common bile duct.

FIGURE 2.

A, Predominant (>75%) tubular growth was observed in 20% of the cases. Typically these were composed of compact, back-to-back tubular elements with minimal or no intervening stroma between the units. In this case, the duct is filled with a neoplastic lesion whereas the duodenal mucosa is spared by the process. Note that the overall picture is quite similar to intraductal tubulopapillary neoplasms of the pancreas. B, Predominant (>75%) papillary pattern was observed in 23% of the lesions. These were characterized with well-formed papillae projecting into the intra-ampullary ducts.

FIGURE 3.

Variable grades of dysplasia could be seen in intra-ampullary papillary-tubular neoplasms, both within the group but also in a given case. Picture on the left illustrates a focus of low-grade dysplasia whereas those in the middle and the right exhibit transition to high-grade dysplasia, which was noted, at least focally, in 96% of the cases. These were characterized with significant architectural atypia with disorganization of cells and loss of polarity, as well as nuclear atypia, including pleomorphism, nuclear irregularities, and hyperchromatism.

FIGURE 4.

Almost half of the cases (45%) were found to have mixed cell-lineage morphology, depicted in this photomicrograph as intestinal (INT; on the left) and gastric/pancreatobiliary (GPB; on the right), both from the same case.

FIGURE 5.

A, Intestinal-type intra-ampullary papillary-tubular neoplasms were similar to conventional colonic/duodenal tubular adenomas consisting of relatively simple villous or tubular glandular units, lined by tall columnar cells with pseudostratified cigar-shaped nuclei. B, Goblet cells were prominent in some cases, and endocrine-type cells with distinctive granules could also be seen.

FIGURE 6.

A, Most gastro-pancreatobiliary-subtype intra-ampullary papillary-tubular neoplasms, similar to pancreatobiliary-type intraductal papillary-mucinous neoplasm in the pancreas, revealed papillary pattern, although some had tubulopapillary growth. B, Gastric-tubular subtype of gastric/pancreatobiliary phenotype was characterized by an exclusive tubular growth pattern. More importantly, the glands were arranged back-to-back and lined by a single layer of cuboidal-to-columnar cells with basally oriented nuclei and abundant apical cytoplasm with mucin, exhibiting cytologic features very similar to gastric pyloric glands or Brunner glands. Despite the relatively bland appearance of the overall lesion, this case was associated with invasive carcinoma.

FIGURE 7.

Invasive carcinomas were generally of tubular-type and were subclassified as pure intestinal (8%; left), pure pancreatobiliary type (20%; right), or mixed (72%; middle). Most cases with “mixed” features were classifiable as intestinal when a forced-binary (favored) approach was used.

FIGURE 8.

Most of intestinal type papillae revealed CDX2 (92%) and MUC2 (85%) expression; however, the specificity of these markers for this phenotype was fairly low (61% and 78%, respectively). In contrast, all pancreatobiliary subtype papillae (100%) were, at least focally, positive for MUC5AC and all gastric-tubular subtype papillae (100%) were, at least focally, positive for MUC1.

FIGURE 9.

A, Immunoprofile of intestinal (INT)-type IAPN, preinvasive component. B, Immunoprofile of gastric/pancreatobiliary (GPB)-type IAPN, preinvasive component. CK, cytokeratin; IAPN, intra-ampullary papillary-tubular neoplasm.

FIGURE 10.

Comparison of invasive IAPNs with conventional invasive carcinomas of the ampulla (unaccompanied with IAPN): Although, the mean survival time was 51 vs. 31 months ($P < 0.001$) and the 3-year survival rate was 69% vs. 44% ($P < 0.01$), the difference in 5-year survival rate (45% vs. 28%) did not reach statistical significance ($P = 0.06$).

TABLE 1

Summary of Immunohistochemical Antibodies

Antigen	Dilution	Retrieval	Source
MUC1	1:160	Citrate	Leica, Microsystems; Bannockburn, IL
MUC2	1:100	Citrate	Leica, Microsystems; Bannockburn, IL
MUC5AC	1:200	Trilog	Leica, Microsystems; Bannockburn, IL
MUC6	1:80	Trilog	Leica, Microsystems; Bannockburn, IL
CDX2	1:200	Citrate	Biogenex, San Ramon, CA
CK7	1:40	Citrate	DAKO, Carpintera, CA
CK20	1:40	Citrate	DAKO, Carpintera, CA

CK indicates cytokeratin.

TABLE 2

General Characteristics of the Cases With and Without Invasive Component

	Overall	Noninvasive	Invasive	P
N	82	18	64	—
Mean age (y)	64	63	64	0.91
Sex (male/female ratio)	2.4	3.5	2.2	0.44
Mean tumor size (cm)	2.7	2.1	2.8	0.04
Growth pattern (%)				
Papillary	23	33	20	0.25
Tubulopapillary+tubular	57+20	50+17	60+20	
High-grade dysplasia (%)				
None+focal	6+39	27+39	0+39	0.04
Substantial+extensive	28+27	17+17	31+30	
Cell lineage of preinvasive component (%)				
INT	74	78	73	0.71
GPB	26	22	27	
3-year survival rate (%)	73	100	69	0.08
5-year survival rate (%)	49	100	45	0.07
Overall survival rate (%)	64	93	57	0.01

GPB indicates gastric/pancreatobiliary; INT, intestinal.

TABLE 3

Histologic Growth Pattern

	Tubulo-papillary	Papillary	Tubular	P
N (%)	47 (57)	19 (23)	16 (20)	
Mean tumor size (cm)	2.9	2.4	2.4	NS
High-grade dysplasia (%)				
None+focal	6+49	5+11	6+44	<0.05
Substantial+extensive	26+19	37+47	25+25	<0.01
Invasive carcinoma (%)	81	68	81	NS
High tumor stage (T3+T4) (%)	11	5	2	NS
Lymph node involvement (%)	20	24	36	NS
3-year survival rate (%)	70	75	80	NS
5-year survival rate (%)	46	60	43	NS
Overall survival rate (%)	61	69	64	NS

NS indicates not significant.

TABLE 4

High-grade Dysplasia

	None+ Focal	Substantial+ Extensive	<i>P</i>
N (%)	5+32 (6+39)	23+22 (28+27)	
Mean tumor size (cm)	2.7	2.7	0.91
Invasive carcinoma (%)	68	87	0.04
High tumor stage (T3+T4) (%)	5	16	0.14
Lymph node involvement (%)	20	26	0.58
3-year survival rate (%)	84	62	0.09
5-year survival rate (%)	63	36	0.09
Overall survival rate (%)	71	56	0.18

TABLE 5

Predominate Cell Lineages in Preinvasive Component

	INT	GPB		P
		PB-papillary	Gastric-tubular	
N (%)	61 (74)	16 (20)	5 (6)	
Mean tumor size (cm)	2.7	2.7	2.3	NS
Growth pattern (%)				
Papillary	11	75	0	<0.001
Tubulopapillary and tubular	66+23	25+0	60+40	
High-grade dysplasia (%)				
None+focal	7+52	0+0	20+0	<0.001
Substantial+extensive	30+11	25+75	20+60	
Invasive carcinoma (%)	77	81	80	NS
Mean invasion size (cm)	1.4	1.5	0.9	NS
Invasion size (%):				
<0.5 cm+0.5-1 cm	13+30	0+38	0+75	NS
>1 cm	57	62	25	NS
Type of invasive carcinoma (%):				
INT	79	0	0	<0.001
GPB	21	100	100	<0.05
High tumor stage (T3+T4) (%)	13	6	0	NS
Lymph node involvement (%)	24	20	33	NS
3-year survival rate (%)	74	71	50	NS
5-year survival rate (%)	55	33	0	NS
Survival rate (%)	63	71	50	NS

GPB indicates gastric/pancreatobiliary; INT, intestinal; NS indicates not significant; PB, pancreaticobiliary.

TABLE 6
Univariate Analysis of Prognostic Factors on Patients With an Associated Invasive Carcinoma

Factors	(%)	P
Age (y)	—	0.58
Sex	Male versus female	68 0.16
Tumor size (cm)	—	0.41
Invasion size (cm)	1 ≤ versus >1	64 0.29
Histologic grade of invasion	G2-3 versus G1	25 0.28
Cell lineage of preinvasive component	Non-INT versus INT	26 0.73
Cell lineage of invasive component	Non-INT versus INT	43 0.71
Growth pattern of invasion	Infiltrative versus expansile	21 0.08
Intraductal spread	Prominent versus no/minimum	11 0.85
Tumor budding	High versus low	60 0.03
Lymphatic invasion	Present versus absent	53 0.31
Venous invasion	Present versus absent	13 0.06
Perineural invasion	Present versus absent	15 0.44
Tumor stage	T3+T4 versus T1+T2	17 <0.01
Lymph node involvement	Present versus absent	28 0.01
Resection margin	Positive versus negative	2 0.99

INT indicates intestinal.

TABLE 7

Multivariate Analysis of Prognostic Factors on Patients With an Associated Invasive Carcinoma

Factors	Groups	HR	95% CI	P
Tumor stage	0: T1+T2 1: T3+T4	4.35	1.34-14.09	0.01
Tumor budding	0: low 1: high	2.57	0.87-7.56	0.09
Venous invasion	0: absent 1: present	2.21	0.70-6.98	0.18
Lymph node involvement	0: absent 1: present	1.40	0.42-4.62	0.58
Growth pattern of invasion	0: expansile 1: infiltrative	0.84	0.24-2.87	0.78

CI indicates confidence interval; HR, Hazard ratio.

TABLE 8

Comparison of IAPNs With an Associated Invasive Carcinoma and Conventional Invasive Carcinomas of the Ampulla

Cases	IAPNs	Others	<i>P</i>
N	64	166	—
Mean age (y)	64	65	0.40
Sex (male/female ratio)	2.2	1.3	0.11
Mean tumor size (cm)	2.8	2.5	0.11
Invasion size (cm)	1.4	1.9	<0.001
Prominent preinvasive component (%)	100	50	<0.001
Tumor grade, well differentiated (%)	77	43	<0.001
Cell lineage, INT type (%)	58	25	<0.001
Lymph node involvement (%)	24	42	0.05
Tumor stage, T1+T2 (%)	86	58	<0.001
Margins, positive (%)	3	6	0.42
Mean survival (mo)	51	31	<0.001
3-year survival rate (%)	69	44	<0.01
5-year survival rate (%)	45	28	0.06
Overall survival rate (%)	57	54	0.71

IAPNs indicates intra-ampullary papillary-tubular neoplasm; INT, intestinal.