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Original contribution

# High-grade precursor lesions can be used as surrogate markers to identify the epicenter of periampullary carcinomas☆,☆☆

**Byung-Kwan Jeong MD[a], You Na Sung MD[a], Sung Joo Kim MD[a], Soyeon An MD[b], Hosub Park MD[a], Hee Sang Hwang MD, PhD[a], Hyo Jeong Kang MD, PhD[a], Jae Hoon Lee MD, PhD[c], Ki Byung Song MD, PhD[c], Kyu-pyo Kim MD, PhD[d], Dae Wook Hwang MD, PhD[c], Sang Soo Lee MD, PhD[e], Song Cheol Kim MD, PhD[c], Seung-Mo Hong MD, PhD[a,*]**

[a]*Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, 05505, Republic of Korea*
[b]*Department of Pathology, Incheon St Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, 21431, Republic of Korea*
[c]*Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, 05505, Republic of Korea*
[d]*Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, 05505, Republic of Korea*
[e]*Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, 05505, Republic of Korea*

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Cancer

**Summary** Identifying the accurate origin of periampullary cancers is important because different origins may trigger different clinicopathological behaviors. The presence of intraepithelial precursor lesions, including high-grade pancreatic intraepithelial neoplasias (PanINs) and/or high-grade biliary intraepithelial neoplasias (BilINs), may be suggestive of the origin of the periampullary carcinoma in challenging cases. To prove the usefulness of high-grade intraepithelial precursor lesions in identifying the origin of ambiguous periampullary cancers, the status and grades of PanINs and BilINs were evaluated in 256 periampullary carcinomas with a well-defined cancer origin as a test set, including 114 pancreatic cancers, 82 distal bile duct cancers, 54 ampullary cancers, and 6 duodenal cancers. One hundred twelve periampullary carcinomas with clinically equivocal epicenter either by radiologic imaging or by endoscopic finding used as a validation set. High-grade PanINs were found more commonly in pancreatic cancers than in distal bile duct, ampullary, and duodenal cancers both in test ($P = .002$) and validation sets ($P < .001$). Similarly, high-grade BilINs were identified more frequently in distal bile duct cancers than in ampullary, pancreatic, and duodenal cancers both in test ($P < .001$) and validation sets ($P = .039$). High-grade PanINs were found most commonly in

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* Corresponding author at: Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
*E-mail address:* smhong28@gmail.com (S. -M. Hong).

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pancreatic cancers, whereas high-grade BilINs were seen most frequently in distal bile duct cancers. In addition, both high-grade PanINs and high-grade BilINs are uncommonly noted in ampullary or duodenal cancers. The recognition of high-grade intraepithelial lesions can help identify the primary origin of periampullary cancers, especially when the epicenter of the periampullary cancer is ambiguous.
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## 1. Introduction

The ampulla of Vater is an anatomically complex region at the confluence of the pancreatic duct, the common bile duct, and the duodenum. Adenocarcinomas arising in periampullary regions, including those of the pancreatic head, the distal common bile duct, the ampulla of Vater, and the duodenum, show different clinicopathological behaviors and prognosis. In general, patients with pancreatic ductal adenocarcinomas have had worse survival rates compared with those with cancer of the distal bile duct, the ampulla of Vater, and the duodenum [1]. Therefore, identifying the precise epicenter of the periampullary carcinoma is important for the proper treatment and prognosis of patients.

Several radiologic imaging criteria, including the morphologic features of the lesion, the size of the mass, the presence of papillary bulging, dilatation of either the biliary duct or the pancreatic duct or both ducts (double-duct sign), and an intraductal polypoid mass, have been used for the clinical determination of periampullary cancers [2,3]. However, determining the epicenter of periampullary tumors based on imaging is still challenging because of the complicated anatomy of the periampullary region. In addition, physiologic contractions of the sphincter of Oddi and the presence of a small volume of fluid in both the bile duct and the pancreatic duct make radiologic evaluation difficult [3,4]. Therefore, the precise determination of the epicenter of periampullary carcinomas depends on pathologic examination. However, when the periampullary carcinoma involves adjacent structures, determining the precise epicenter becomes even more difficult in daily pathologic practice. Distal bile duct cancer and pancreatic head cancer are particularly hard to distinguish from each other because of their histopathologic similarity, including the presence of tubular adenocarcinomas with a desmoplastic reaction of the adjacent stroma [5]. Moreover, tumor markers that are currently in use are unable to distinguish these tumor types. For example, commonly used immunohistochemistry markers, such as cytokeratin 7, CEA, and CA 19–9, are expressed in both pancreatic and distal bile duct cancers [6,7]. These phenotypic resemblances may result from the common embryologic origin (ventral pancreatic bud) of periampullary structures, such as the pancreatic head and the distal bile duct [8].

The eighth edition of the American Joint Committee of Cancer (AJCC) staging classification of distal bile duct cancer has recently introduced changes in T categories, which are now defined based on invasion depth as T1, less than 5 mm; T2, 5 to 12 mm; and T3, greater than 12 mm, instead of anatomic landmarks, such as the involvement of other adjacent organs, used in the previous staging system [9,10]. On the other hand, the eighth edition of the AJCC staging classification of pancreatic cancer classified T categories based on tumor size as T1, 2 cm or less; T2, greater than 2 and 4 cm or less; and T3, greater than 4 cm, instead of the involvement of other adjacent organs used in the previous staging system [9,10]. These changes allow for better discrimination between distal bile duct and pancreatic cancers because the new staging systems for the 2 organs are more distinct.

Pancreatic intraepithelial neoplasias (PanINs) are the most common intraductal precursor lesions of pancreatic ductal adenocarcinomas, and a 3-tier grading system (PanIN-1, PanIN-2, and PanIN-3) has been used for several decades to classify them [11,12]. Recently, a 2-tier system (low and high grades) was proposed by the Baltimore consensus meeting to grade the degree of dysplasia [13]. High-grade PanINs are observed more commonly adjacent to pancreatic ductal adenocarcinomas than to normal pancreas [14]. Similarly, biliary intraepithelial neoplasias (BilINs) are known as intraductal precursor lesions of intrahepatic and extrahepatic cholangiocarcinomas, and a 3-tier grading system (BilIN-1, BilIN-2, and BilIN-3) has been used to classify them according to the degree of cytologic and architectural atypia [15]. BilINs are thought to occur in pathways of multistep carcinogenesis toward cholangiocarcinoma similar to the progression of PanINs to pancreatic ductal adenocarcinomas [15,16]. After the modification of the 2-tier system for PanINs, the use of a 2-tier system for BilINs (low and high grades) is now suggested [17].

The aim of this study was to find possible roles for PanINs or BilINs in identifying the epicenter of periampullary carcinomas. We investigated the presence of PanINs and/or BilINs in adenocarcinomas of the pancreatic duct, the distal bile duct, the ampulla of Vater, and the duodenum and their association with other clinicopathological factors.

## 2. Materials and methods

### 2.1. Case selection

Approval from the institutional review board (protocol no. 2014–6591) and a waiver of consent from the patients

were obtained. Surgically resected consecutive periampullary carcinoma cases of patients who underwent either pancreaticoduodenectomy (Whipple operation) or pylorus-preserving pancreaticoduodenectomy at the Department of Surgery, Asan Medical Center, from January 2014 to December 2014, were retrieved from the Pathology Database. Cases diagnosed with tubular adenocarcinomas of the pancreas, the distal bile duct, the ampulla of Vater, and the duodenum were included as a test set. On the other hand, carcinomas with special histologic subtypes, such as ductal adenocarcinomas arising from intraductal papillary neoplasms of the pancreas, cholangiocarcinomas arising from intraductal papillary neoplasms of the bile duct, adenosquamous carcinomas, squamous cell carcinomas, undifferentiated carcinomas, and neuroendocrine carcinomas, were excluded. One hundred twelve periampullary carcinomas with clinically equivocal epicenter by radiologic imaging or by endoscopic finding, but cases diagnosed with tubular adenocarcinomas of the pancreas, the distal bile duct, the ampulla of Vater, and the duodenum after histopathologic examination from January 2014 to December 2017 were selected as a validation set. Finally, a total of 368 periampullary adenocarcinomas, including 256 cases with an unequivocal epicenter of origin and 112 cases with clinically equivocal epicenter of origin, were included in our study.

## 2.2. Histopathologic evaluation

At first, the involved organs of all cases were classified according to the location of the tumor epicenter by gross examination. One hundred twelve periampullary carcinoma cases with clinically equivocal epicenter including cases with discrepancies between radiologic and/or endoscopic findings and pathologic diagnosis regarding the location, or cases with ambiguous results about the epicenters on gross examinations were further evaluated by microscopic examination (Supplementary Table 1).

When the epicenter of a tumor was located within the ampullary region or the wall of the distal common bile duct regardless of the involvement of the pancreatic duct, at the papilla of Vater on the junction of the ampullary and duodenal mucosa, or at the duodenal surface of the papilla of Vater, the tumor was classified as a primary ampullary tumor, which has been described elsewhere [6]. When the tumor symmetrically and circumferentially involved the distal common bile duct regardless of the eccentric involvement of the pancreas, it was considered as a primary distal common bile duct cancers [18]. On the other hand, when the tumor mainly involved the pancreatic parenchyma regardless of the focal or asymmetrical involvement of the distal common bile duct, it was classified as a primary pancreatic cancer [18]. When the tumor was located in the duodenum without the involvement of the papilla of Vater, it was categorized as a primary duodenal cancer. Cases not meeting the aforementioned criteria were excluded from this study.

To evaluate the status of intraepithelial lesions, slides of all 368 cases were reviewed to select sections containing both pancreatic parenchyma and distal common bile ducts. Three to 11 hematoxylin and eosin–stained slides from each case (mean, 5.9±1.6 slides per case) were selected and reviewed by 2 pathologists (B. K. J. and S. M. H.).

PanINs are defined as microscopic noninvasive, flat or papillary, epithelial neoplasms, which are confined to the pancreatic ducal system, usually less than 0.5 cm in diameter [11,12]. Similarly, BilINs are defined as nonpapillary premalignant lesions or in situ neoplastic lesions of the biliary ductal system [15].

When pancreatobiliary intraepithelial lesions, either PanINs or BilINs, were present, they were further classified as low-grade (low-grade BilINs or low-grade PanINs) or high-grade (high-grade BilINs or high-grade PanINs) dysplastic lesions [15]. Briefly, when a small precursor lesion showed the highest degree of structural and cytologic atypia, it was classified as a high-grade dysplastic lesion (either high-grade BilIN or high-grade PanIN).

High-grade PanINs (previously classified as PanIN-3) are typically papillary lesions with loss of polarity, irregular nuclear stratification, tufting, necrosis, marked cytologic atypia, and mitoses [11,12]. Similarly, high-grade BilINs (previously classified as BilIN-3) are typically pseudopapillary or micropapillary lesions with cytoplasmic budding, cribriform-patterned architecture, loss of polarity, irregular nuclear stratification, and marked nuclear membranous irregularities, and severe cytologic and nuclear atypia [15]. In contrast, when a structural and cytologic abnormality did not show the highest degree of atypia, it was classified as a low-grade dysplastic lesion (either low-grade BilIN or low-grade PanIN). Because it was histologically impossible to discriminate between high-grade PanINs and intraductal spreading of ductal adenocarcinoma of the pancreas or between high-grade BilINs and intraductal spreading of distal cholangiocarcinomas, cases showing high-grade dysplasia were considered as either high-grade PanINs or high-grade BilINs [19]. Representative images of PanINs or BilINs are depicted in Fig. 1. Patients who received neoadjuvant chemotherapy were also excluded.

Clinical data, including sex and age of the patients, chief presenting symptoms, and recurrence status, were collected in electronic medical records. Pathologic information, including tumor size and differentiation, AJCC cancer staging [9], lymphovascular and perineural invasion, and lymph node metastasis, was also collected.

## 2.3. Statistical analysis

Statistical analysis was performed using SPSS 23.0 for Windows (SPSS, Chicago, IL). Categorical variables were analyzed using the $\chi^2$ test. Continuous variables were compared using the unpaired Student $t$ test. The Kaplan-Meier method was used to evaluate recurrence-free survival, whereas the association between recurrence-free survival and

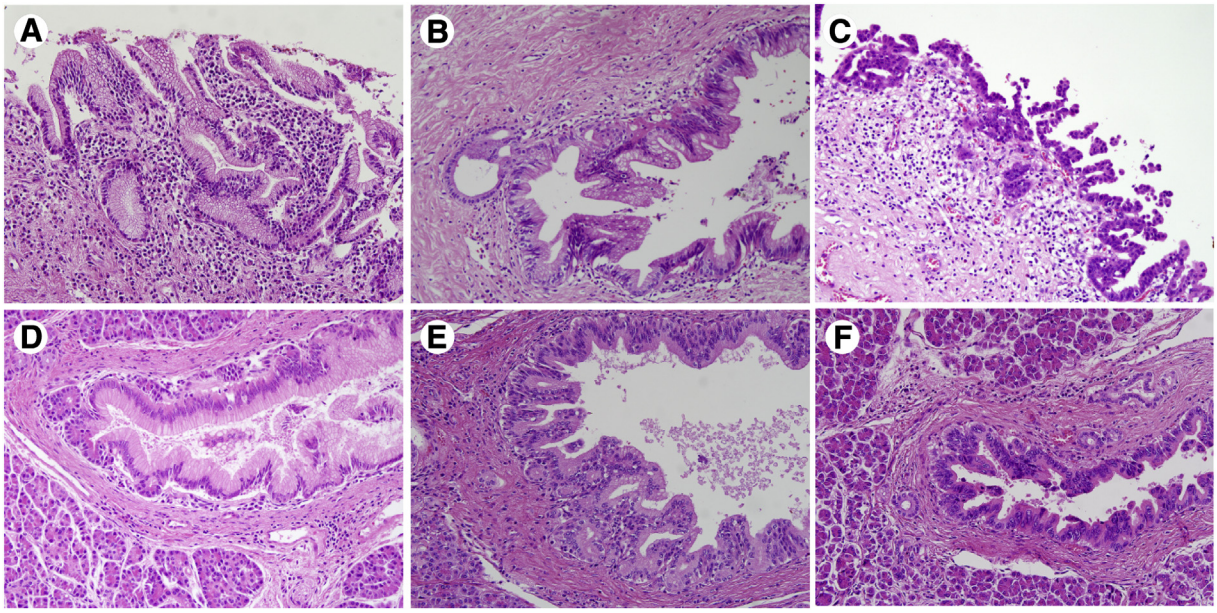


**Fig. 1** Representative hematoxylin and eosin images of pancreatobiliary precursor lesions of periampullary cancers. A, Low-grade BilIN (previous BilIN-1) shows mild nuclear atypia including membrane irregularity without disturbance of cellular polarity. B, Low-grade BilIN (previous BilIN-2) shows focal disturbance of cellular polarity and nuclear crowding. C, High-grade BilIN (previous BilIN-3) shows diffuse disturbance of cellular polarity and micropapillary feature. D, Low-grade PanIN (previous PanIN-1) shows mucin-containing columnar epithelial cells with basally oriented, uniform, round nuclei. E, Low-grade PanIN (previous PanIN-2) shows focal loss of cellular polarity, nuclear crowding, and pseudostratification. F, High-grade PanIN (previous PanIN-3) shows pleomorphic nuclei with loss of polarity and micropapillary architecture. A-F, Original magnification ×200.

clinicopathological factors was evaluated using the log-rank test. The Cox proportional hazards regression model was used to investigate the significance of clinicopathological factors as prognostic factors. Values of $P < .05$ were considered statistically significant. Receiver operating characteristic (ROC) curves for the presence of BilIN or PanIN were drawn. The

**Table 1** Clinicopathological characteristics of 368 periampullary cancer cases

| Baseline characteristic | Total (n = 368) | Periampullary cancer with unequivocal epicenter (test set, n = 256) | Periampullary cancer with clinically equivocal epicenter (validation set, n = 112) |
|---|---|---|---|
| Patient age (y), median (range) | 64 (34-82) | 64 (36-82) | 64 (34-82) |
| Sex, n (%) | | | |
| Male | 222 (60.3) | 165 (64.5) | 57 (50.9) |
| Female | 146 (39.7) | 91 (35.5) | 55 (49.1) |
| Origin of tumor, n (%) | | | |
| Pancreas | 173 (47.0) | 114 (44.5) | 59 (52.7) |
| Distal common bile duct | 89 (24.2) | 82 (32.0) | 7 (6.3) |
| Ampulla of Vater | 95 (25.8) | 54 (21.1) | 41 (36.6) |
| Duodenum | 11 (3.0) | 6 (2.3) | 5 (4.5) |
| Tumor size, n (%) | | | |
| <2.5 cm | 150 (40.8) | 104 (40.6) | 46 (41.1) |
| ≥2.5 cm | 218 (59.2) | 152 (59.4) | 66 (58.9) |
| Perineural invasion, n (%) | 266 (72.3) | 192 (75) | 74 (66.1) |
| Lymphovascular invasion, n (%) | 232 (63.0) | 153 (59.8) | 79 (70.5) |
| Node metastasis, n (%) | 184 (50.0) | 128 (50) | 56 (50) |
| Differentiation, n (%) | | | |
| Well differentiated | 53 (14.4) | 32 (12.5) | 21 (18.8) |
| Moderately differentiated | 273 (74.2) | 188 (73.4) | 85 (75.8) |
| Poorly differentiated | 42 (11.4) | 36 (14.1) | 6 (5.4) |

**Table 2** Comparisons of clinicopathological characteristics and pancreatobiliary intraepithelial lesions in periampullary cancer cases with unequivocal epicenter (test set)

| Characteristics | PanIN | *P* | High-grade PanIN | *P* | BilIN | *P* | High-grade BilIN | *P* |
|---|---|---|---|---|---|---|---|---|
| Origin | | | | | | | | |
| Pancreas | 73/114 (64.0%) | <.001 * | 25/114 (21.9%) | .02 * | 30/114 (26.3%) | <.001 * | 11/114 (9.6%) | <.001 * |
| Distal common bile duct | 26/82 (31.7%) | | 7/82 (8.5%) | | 60/82 (73.2%) | | 46/82 (56.1%) | |
| Ampulla of Vater | 32/54 (59.3%) | | 5/54 (9.3%) | | 31/54 (57.4%) | | 13/54 (24.1%) | |
| Duodenum | 1/6 (16.7%) | | 0/6 (0.0%) | | 0/6 (0/0%) | | 0/6 (0.0%) | |
| Sex | | | | | | | | |
| Male | 83/165 (50.3%) | .493 | 25/165 (15.2%) | .669 | 80/165 (48.5%) | .818 | 45/165 (27.3%) | .973 |
| Female | 49/91 (53.8%) | | 12/91 (13.2%) | | 41/91 (45.1%) | | 25/91 (27.5%) | |
| Age | | | | | | | | |
| <64 y | 59/118 (50%) | .953 | 18/118 (15.3%) | .736 | 52/118 (44.1%) | .504 | 28/118 (23.7%) | .23 |
| ≥64 y | 73/138 (52.9%) | | 19/138 (13.8%) | | 69/138 (50.0%) | | 42/138 (30.4%) | |
| Tumor size | | | | | | | | |
| <2.5 cm | 61/103 (59.2%) | .211 | 17/103 (16.5%) | .444 | 50/103 (48.5%) | .833 | 27/103 (26.2%) | .739 |
| ≥2.5 cm | 71/153 (46.4%) | | 20/153 (13.1%) | | 71/153 (46.4%) | | 43/153 (28.1%) | |
| pT category | | | | | | | | |
| T1-T2 | 27/67 (40.3%) | .027 * | 4/67 (6.0%) | .022 * | 45/67 (67.2%) | .002 * | 28/67 (41.8%) | .002 * |
| T3-T4 | 105/189 (55.6%) | | 33/189 (17.5%) | | 76/189 (40.2%) | | 42/189 (22.2%) | |
| LN metastasis | | | | | | | | |
| Absent | 57/128 (44.5%) | .028 * | 11/128 (8.6%) | .008 * | 69/128 (53.9%) | .185 | 40/128 (31.3%) | .161 |
| Present | 75/128 (58.6%) | | 26/128 (20.3%) | | 52/128 (40.6%) | | 30/128 (23.4%) | |
| Lymphovascular invasion | | | | | | | | |
| Absent | 52/103 (50.5%) | .075 | 8/103 (7.8%) | .013 * | 47/103 (45.6%) | .848 | 27/103 (26.2%) | .739 |
| Present | 80/153 (52.3%) | | 29/153 (19.0%) | | 74/153 (48.4%) | | 43/153 (28.1%) | |
| Perineural invasion | | | | | | | | |
| Absent | 33/64 (51.6%) | .058 | 8/64 (12.5%) | .608 | 37/64 (57.8%) | .093 | 18/64 (28.1%) | .871 |
| Present | 99/192 (51.6%) | | 29/192 (15.1%) | | 84/192 (43.8%) | | 52/192 (27.1%) | |

* Statistically significant difference is indicated as $P < .05$.

variables were considered to be predictive when both the lower and upper bounds of asymptotic 95% confidence intervals of area-under-curve (AUC) values were greater than .5.

## 3. Results

### 3.1. Clinicopathological characteristics of the cases

Of the 317 patients diagnosed as having adenocarcinoma of the pancreas, the distal common bile duct, the ampulla of Vater, or the duodenum at the Asan Medical Center in 2014, 30 patients undergoing total pancreatectomy due to extensive pancreatic spread after distal pancreatectomy resulting from the pancreatic tail origin of the tumor were excluded from the analyses. Another 3 patients who received neoadjuvant chemotherapy before the surgical resection were also excluded. Finally, 256 periampullary cancer cases with an unequivocal epicenter of origin in the pancreas, the distal common bile duct, the ampulla of Vater, or the duodenum were selected as the test set. In addition, 112 periampullary cases with equivocal origin were included as the validation set.

The characteristics of the cases of the both test and validation set are summarized in Table 1. Briefly, the mean patient age at diagnosis of the test set was 63.9±9.5 years with a male-to-female ratio of 1.8. Tumors were located in the pancreas in 114 cases (45%), in the distal common bile duct in 82 cases (32%), in the ampulla of Vater in 54 cases (21%), and in the duodenum in 6 cases (2%). The mean tumor size was 2.8±1.1 cm (median, 2.5 cm; range, 0.6-8.2 cm). Lymphovascular and perineural invasion was observed in 153 (60%) and 192 (75%) cases, respectively. Lymph node metastasis was observed in 128 cases (50%). The differentiation of the majority of tumors was moderately differentiated (73%).

Similarly, the mean patient age at diagnosis of the validation set of periampullary carcinomas with clinically equivocal epicenter was 64.2±10.2 years with a male-to-female ratio of 1.0. Tumors were located in the pancreas in 59 cases (53%), in the distal common bile duct in 7 cases (6%), in the ampulla of Vater in 41 cases (37%), and in the duodenum in 5 cases (5%). The mean tumor size was 2.7±1.1 cm (median, 2.5 cm; range, 0.6-6.2 cm). Lymphovascular and perineural invasion was observed in 79 (71%) and 74 (66%) cases, respectively. Lymph node metastasis was observed in 56 cases (50%). The differentiation of the majority of tumors was moderately differentiated (76%).

**Table 3** Comparisons of clinicopathological characteristics and pancreatobiliary intraepithelial lesions in periampullary cancer cases with clinically equivocal epicenter (validation set)

| Characteristics | PanIN | *P* | High-grade PanIN | *P* | BilIN | *P* | High-grade BilIN | *P* |
|---|---|---|---|---|---|---|---|---|
| Origin | | | | | | | | |
| Pancreas | 46/59 (78.0%) | <.001 * | 21/59 (35.6%) | <.001 * | 13/59 (22.0%) | .013 * | 2/59 (3.4%) | .068 |
| Distal common bile duct | 6/7 (85.7%) | | 0/7 (0%) | | 6/7 (85.7%) | | 2/7 (28.6%) | |
| Ampulla of Vater | 20/41 (48.8%) | | 1/41 (2.4%) | | 19/41 (46.3%) | | 5/41 (12.2%) | |
| Duodenum | 2/5 (40.0%) | | 0/5 (0.0%) | | 0/5 (0/0%) | | 0/5 (0.0%) | |
| Sex | | | | | | | | |
| Male | 36/57 (63.2%) | .873 | 10/57 (17.5%) | .569 | 19/57 (33.3%) | .971 | 4/57 (7.0%) | .687 |
| Female | 38/55 (69.1%) | | 12/55 (21.8%) | | 19/55 (34.5%) | | 5/55 (9.1%) | |
| Age | | | | | | | | |
| <64 y | 28/49 (57.1%) | .038 * | 4/49 (8.2%) | .007 * | 15/49 (30.6%) | .533 | 4/49 (8.2%) | .965 |
| ≥64 y | 46/63 (73.0%) | | 18/63 (28.6%) | | 23/63 (36.5%) | | 5/63 (7.9%) | |
| Tumor size | | | | | | | | |
| <2.5 cm | 29/46 (63.0%) | .607 | 11/46 (23.9%) | .342 | 21/46 (45.7%) | .018 * | 2/46 (4.3%) | .231 |
| ≥2.5 cm | 45/66 (68.2%) | | 11/66 (16.7%) | | 17/66 (25.8%) | | 7/66 (10.6%) | |
| pT category | | | | | | | | |
| T1-T2 | 11/25 (44.0%) | .030 * | 1/25 (4.0%) | .026 * | 11/25 (44.0%) | .293 | 4/25 (16.0%) | .097 |
| T3-T4 | 63/87 (72.4%) | | 21/87 (24.1%) | | 27/87 (31.0%) | | 5/87 (5.7%) | |
| LN metastasis | | | | | | | | |
| Absent | 32/56 (57.1%) | .060 | 13/56 (23.2%) | .341 | 20/56 (35.7%) | .521 | 3/56 (5.4%) | .297 |
| Present | 42/56 (75.0%) | | 9/47 (19.1%) | | 18/56 (32.1%) | | 6/56 (10.7%) | |
| Lymphovascular invasion | | | | | | | | |
| Absent | 21/33 (63.6%) | .075 | 8/33 (24.2%) | .428 | 13/33 (39.4%) | .636 | 2/33 (6.1%) | .619 |
| Present | 53/79 (67.1%) | | 14/79 (17.7%) | | 25/79 (31.6%) | | 7/79 (8.9%) | |
| Perineural invasion | | | | | | | | |
| Absent | 17/38 (44.7%) | .005 * | 4/38 (10.5%) | .082 | 13/38 (34.2%) | .264 | 5/38 (13.2%) | .153 |
| Present | 57/74 (77.0%) | | 18/74 (24.3%) | | 25/74 (33.8%) | | 4/74 (5.4%) | |

* Statistically significant difference is indicated as $P < .05$.

### 3.2. Intraepithelial lesions in periampullary adenocarcinomas of test set

The clinicopathological features of intraepithelial precursor lesions of the test set with unequivocal epicenter are summarized and compared in Table 2. PanINs were present in 132 of 256 cases (51.6%) and high-grade PanINs (PanIN-3) were noted in 37 cases (14.5%), whereas BilINs were present in 121 cases (47.1%) and high-grade BilINs (BilIN-3) were observed in 70 cases (27.2%). PanINs were observed more commonly in pancreatic (73/114; 64%) or ampulla of Vater (32/54; 59%) cancers than in distal bile duct (26/82; 32%) or duodenal (1/6; 17%) cancers ($P < .001$). PanINs were observed more commonly in periampullary cancer cases with a higher primary tumor (pT) category ($P = .027$) and in the presence of lymph node metastasis ($P = .028$).

High-grade PanINs were found more commonly in pancreatic cancers (25/114; 22%) than in ampulla of Vater (5/54; 9%), distal bile duct (7/82; 9%), or duodenal (0/6; 0%) cancers ($P = .02$). High-grade PanINs were observed more commonly in all periampullary cancers with a higher pT category ($P = .022$ and $P = .026$), in the presence of lymph node metastasis ($P = .008$) or lymphovascular invasion ($P = .013$).

**Table 4** Comparisons of high-grade intraepithelial lesions in periampullary adenocarcinomas with unequivocal epicenter (test set) and the origin of tumors after dichotomization

| Origin | High-grade PanIN | *P* | Origin | High-grade BilIN | *P* |
|---|---|---|---|---|---|
| Pancreas | 25/114 (21.9%) | .002 * | Distal common bile duct | 46/82 (56.1%) | <.001 * |
| Others | 12/142 (8.4%) | | Others | 24/174 (13.7%) | |

* Statistically significant difference is indicated as $P < .05$.

**Table 5** Comparisons of high-grade intraepithelial lesions in periampullary adenocarcinomas with clinically equivocal epicenter (validation set) and the origin of tumors after dichotomization

| Origin | High-grade PanIN | *P* | Origin | High-grade BilIN | *P* |
|---|---|---|---|---|---|
| Pancreas | 21/59 (36%) | <.001 * | Distal common bile duct | 2/7 (29%) | .039 * |
| Others | 1/53 (2%) | | Others | 7/105 (7%) | |

* Statistically significant difference is indicated as P < .05.

BilINs were observed more commonly in distal bile duct (60/82; 73%) or ampulla of Vater (31/54; 57%) cancers both in unequivocal and equivocal cases than in pancreatic (30/114; 26%) or duodenal (0/6; 0%) cancers ($P < .001$). The presence of BilINs was noted more commonly in periampullary cancers and a lower pT category ($P = .002$).

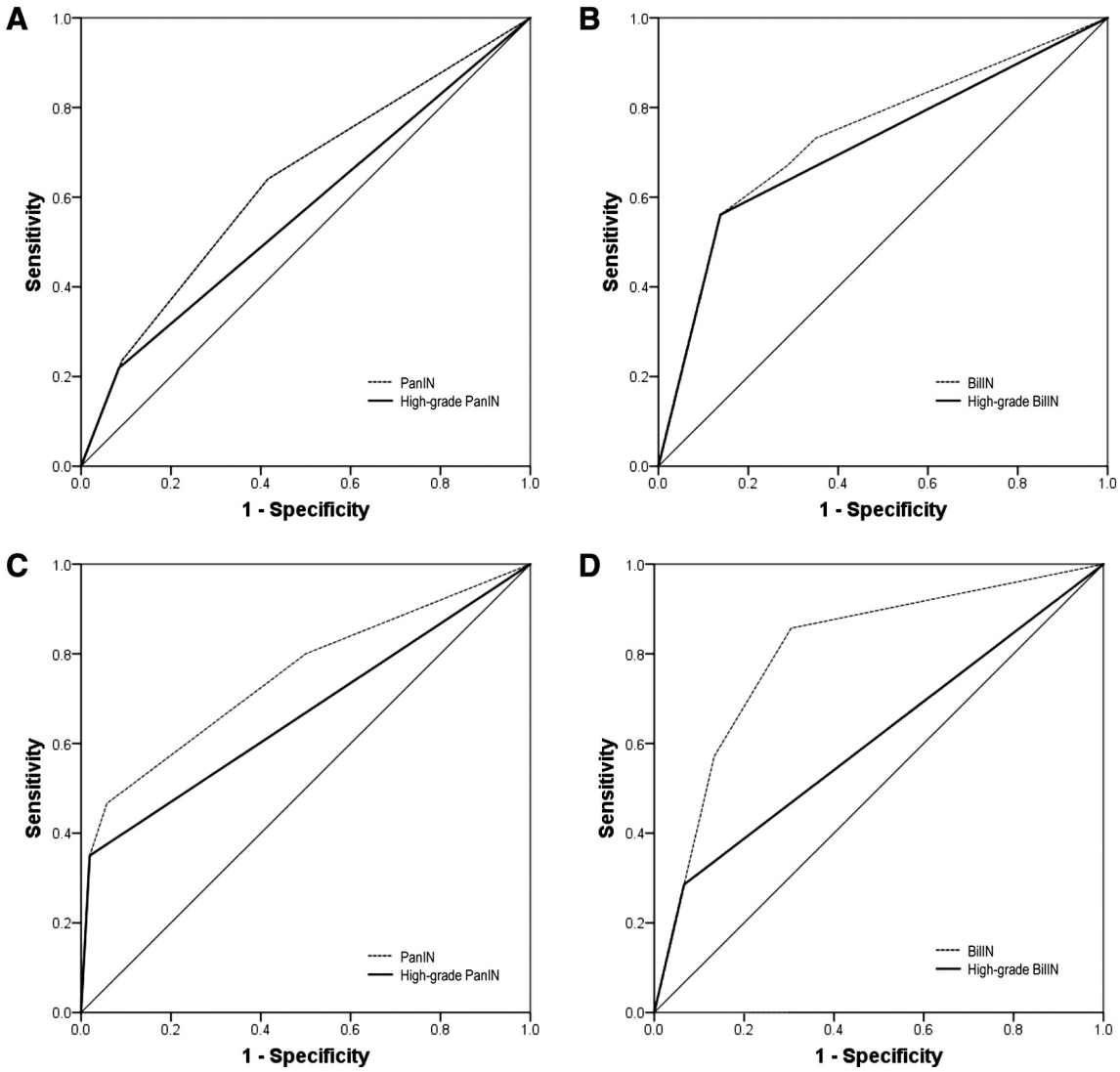


**Fig. 2** ROC curves of the pancreatobiliary intraepithelial lesions to predict the origin of periampullary cancers. A and B, Presence of PanIN/high-grade PanIN (A) and of BilIN/high-grade BilIN (B) are shown to be predictive to discriminate pancreatic and distal bile duct origin cancer, respectively, in periampullary cancers with unequivocal epicenter (for pancreatic origin: AUCs, 0.63 [95% confidence interval, or CI, 0.56-0.70] for PanIN and 0.57 [95% CI, 0.50-0.64] for high-grade PanIN; for distal bile duct origin: AUCs, 0.74 [95% CI, 0.67-0.81] for BilIN and 0.71 [95% CI, 0.64-0.78] for high-grade BilIN). C and D, Presence of PanIN/high-grade PanIN (C) and of BilIN/high-grade BilIN (D) are shown to be predictive to discriminate pancreatic and distal bile duct origin cancer, respectively, in periampullary cancers with clinically equivocal epicenter (for pancreatic origin: AUCs, 0.75 [95% CI, 0.66-0.84] for PanIN and 0.67 [95% CI, 0.57-0.77] for high-grade PanIN). D, BilIN/high-grade BilIN is also predictive for distal bile duct origin in periampullary cancer with equivocal epicenter, but high-grade BilIN exhibits nonsignificant result (BilIN: AUC, 0.81 [95% CI, 0.64-0.97]; high grade BilIN: AUC, 0.61 [95% CI, 0.37-0.85]).

**Table 6** Results from ROC analysis of the intraepithelial lesions to predict the origin of tumor

| Group | Intraepithelial lesion | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | Positive likelihood ratio | Negative likelihood ratio |
|---|---|---|---|---|---|---|---|
| Unequivocal epicenter (test set) | PanIN | 64.0 | 58.5 | 55.3 | 66.9 | 1.54 | 0.62 |
| | High-grade PanIN | 21.9 | 91.6 | 67.6 | 59.4 | 2.60 | 0.85 |
| | BilIN | 73.2 | 64.9 | 49.6 | 83.7 | 2.09 | 0.41 |
| | High-grade BilIN | 56.1 | 86.2 | 65.7 | 80.6 | 4.07 | 0.51 |
| Clinically equivocal epicenter (validation set) | PanIN | 80.0 | 50.0 | 64.9 | 68.4 | 1.60 | 0.40 |
| | High-grade PanIN | 35.0 | 98.1 | 95.5 | 56.7 | 18.20 | 0.66 |
| | BilIN | 85.7 | 69.5 | 15.8 | 98.6 | 2.81 | 0.21 |
| | High-grade BilIN | 100 | 57.1 | 13.5 | 100 | 2.33 | 0.00 |

High-grade BilINs were seen more commonly in distal bile duct cancer (46/82; 56%) than in ampulla of Vater (13/54; 24%), pancreatic (11/114; 10%), or duodenal (0/6; 0%) cancers ($P < .001$). The presence of high-grade BilINs was noted more commonly in periampullary cancers with a lower pT category (P = .002).

## 3.3. Intraepithelial lesions in periampullary adenocarcinomas of validation set

The clinicopathological features of intraepithelial precursor lesions of the validation set with clinically equivocal epicenter are summarized and compared in Table 3. PanINs were present in 74 (66.1%) of 112 cases and high-grade PanINs were noted in 22 cases (19.6%), whereas BilINs were present in 38 cases (33.9%) and high-grade BilINs were observed in 9 cases (8.0%). PanINs were observed more commonly in pancreatic (46/59; 78.0%) or distal bile duct (6/7; 85.7%) cancers than in ampulla (20/41; 48.8%) or duodenal (2/5; 40%) cancers ($P < .001$). PanINs were observed more commonly in periampullary cancer cases with a higher pT category ($P = .030$), in older age ($P = .038$), and in the presence of perineural invasion ($P = .005$).

Similar to test set, high-grade PanINs were more commonly found in pancreatic cancers (21/59; 35.6%) than in ampulla of Vater (1/41; 2.4%), distal bile duct (0/7; 0%), or duodenal (0/5; 0%) cancers ($P < .001$). High-grade PanINs were observed more commonly in all periampullary cancers with a higher pT category ($P = .026$) and in the older age ($P = .007$).

BilINs were observed more commonly in distal bile duct (6/7; 86%) or ampulla of Vater (19/41; 46.3%) cancers than in pancreatic (13/59; 22%) or duodenal (0/5; 0%) cancers ($P = .013$). The presence of BilINs was more commonly noted in smaller tumor size ($P = .018$).

**Table 7** Univariate and multivariate analyses for recurrence-free survival

| Factors | Univariate analysis, HR (95% CI) | *P* | Multivariate, HR (95% CI) | *P* |
|---|---|---|---|---|
| Age (<64 y *vs* ≥64 y) | 1.27 (0.84-1.94) | .261 | – | – |
| Sex (male *vs* female) | 0.76 (0.50-1.16) | .209 | – | – |
| Pancreatic origin | 2.94 (1.93-4.46) | <.001 * | 1.91 (1.22-2.98) | .004 * |
| Size (<2.5 cm *vs* ≥2.5 cm) | 1.58 (1.03-2.42) | .032 * | 1.11 (0.71-1.72) | .656 |
| Perineural invasion | 2.82 (1.62-4.92) | <.001 * | 1.95 (1.09-3.48) | .025 * |
| Lymphovascular invasion | 2.40 (1.53-3.78) | <.001 * | 1.29 (0.80-2.11) | .300 |
| Lymph node metastasis | 3.27 (2.11-5.07) | <.001 * | 2.67 (1.70-4.20) | <.001 * |
| Differentiation | – | .001 * | – | .027 * |
| Well differentiated | 1 | Reference | 1 | Reference |
| Moderately differentiated | 3.28 (1.19-8.98) | .021 * | 1.62 (0.57-4.63) | .368 |
| Poorly differentiated | 6.88 (2.32-20.39) | .001 * | 3.14 (1.01-9.75) | .048 * |
| High-grade PanIN | 1.08 (0.62-1.87) | .795 | – | – |
| High-grade BilIN | 0.70 (0.43-1.14) | .147 | – | – |

Abbreviations: HR, hazard ratio; CI, confidence interval.
* Statistically significant difference is indicated as $P < .05$.

High-grade BilINs tended to be more common in distal bile duct cancer (2/7; 28.6%) than in ampulla of Vater (5/41; 12.2%), pancreatic (2/59; 3.4%), or duodenal (0/5, 0.0%) cancers, but it was not statistical significance ($P = .068$). Presence of high-grade BilINs was noted more commonly in periampullary cancers with a lower pT category ($P = .002$).

### 3.4. Comparisons of intraepithelial lesions in periampullary adenocarcinomas after dichotomization

When we dichotomized primary cancers as pancreatic cancers versus other periampullary cancers (distal bile duct, ampulla of Vater, or duodenum) and investigated the associations with the presence of high-grade intraepithelial lesions (high-grade PanINs and high-grade BilINs), high-grade PanINs were found more commonly in pancreatic cancers both in test and validation sets (test set, 25/114 [22%]; validation set, 21/59 [36%]) than in other periampullary cancers (test set, 12/142 [8%; $P = .002$]; validation set, 1/53 [2%; $P < .001$]; Tables 4 and 5). Similarly, high-grade BilINs were noted more commonly in distal bile duct cancers both in test and validation sets (test set, 46/82 [56%]; validation set, 2/7 [28.6%]) than in other periampullary cancers (test set, 24/174 [14%; $P < .001$; validation set, 7/105 [6.7%; $P = .039$]; Tables 4 and 5).

### 3.5. ROC curve analysis

ROC curves were generated to determine the sensitivity and specificity performance characteristics for diagnosis of periampullary carcinomas with each intraepithelial lesion (Fig. 2 and Table 6). ROC curve analysis revealed that PanIN and high-grade PanIN could serve as valuable histologic markers for distinguishing pancreatic cancers from other periampullary cancers with unequivocal epicenters (area under the curve [AUC], 0.63 for PanIN; AUC, 0. 57 for high-grade PanIN) and with equivocal epicenters (AUC, 0.75 for PanIN; AUC, 0.67 for high-grade PanIN).

Similarly, the ROC curve analysis revealed that BilIN and high-grade BilIN could serve as valuable histologic markers for distinguishing distal bile duct carcinomas from other periampullary cancers with unequivocal epicenters (AUC, 0.74 for BilIN; AUC, 0.71 for high-grade BilIN). In cases with equivocal epicenters, only BilIN was useful with an AUC of 0.81.

### 3.6. Survival analysis of periampullary adenocarcinomas

After excluding 25 patients lost to follow-up immediately after surgery and 47 patients with incomplete resection, 184 patients in the test set were included in the analysis of recurrence-free survival. Patients in the validation set were excluded for survival analysis because of their short follow-up period (mean, 29±15 months). The recurrence-free survival of patients with pancreatic cancer (median, 10 months) was significantly worse than that of patients with other periampullary cancers (medians, 28 months for the distal bile duct, 31 months for the ampulla of Vater, 22 months for the duodenum; $P < .001$; Table 7 and Fig. 3).

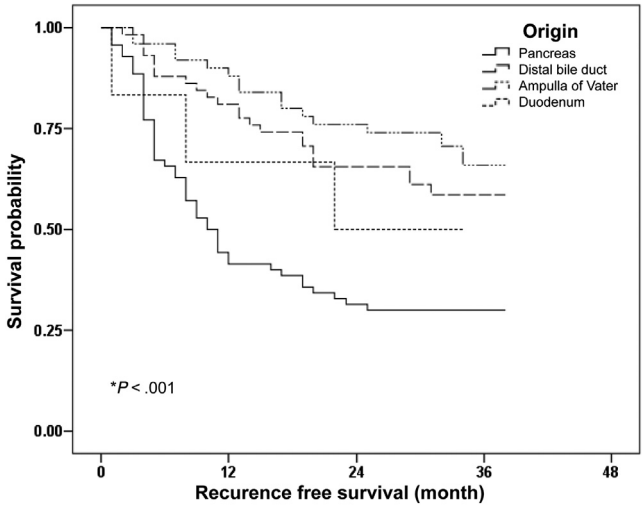


**Fig. 3** Recurrence-free survival comparison among periampullary cancers. Patients with pancreatic cancer had significantly worse recurrence-free survival (median, 10 months) than did those with other periampullary cancers (medians, 28 months for distal bile duct, 31 months for ampulla of Vater, and 22 months for duodenum; $P < .001$).

On the other hand, the presence of high-grade PanINs in patients with periampullary cancer showed no significant impact on recurrence-free survival (medians, 12 months for patients with pancreatic cancer with high-grade PanIN and 8 months for those without high-grade PanIN [$P = .157$; Fig. 4A; medians, 28 months for patients with distal bile duct cancer with high-grade PanIN and 29 months for those without high-grade PanIN [$P = .690$; Fig. 4B]; medians, 31 months for patients with ampulla of Vater cancer with high-grade PanIN and 36 months for those without high-grade PanIN [$P = .865$; Fig. 4C]). Patients with duodenal cancer who did not have any high-grade PanINs were excluded from the interpretation of the results.

Similarly, the presence of high-grade BilINs in patients with periampullary cancers seemed to have no significant impact on recurrence-free survival (medians, 8 months for patients with pancreatic cancer with high-grade BilIN and 11 months for those without high-grade BilIN [$P = .739$; Fig. 4D]; medians, 28 months for patients with distal bile duct cancer with high-grade BilIN and 30 months for those without high-grade BilIN [$P = .436$; Fig. 4E]; medians, 31 months for patients with ampulla of Vater cancer with high-grade BilIN and 31 months for those without high-grade BilIN [$P = .300$; Fig. 4F]). Patients with duodenal cancer were excluded because of the absence of high-grade BilINs.

### 3.7. Univariate analyses of other clinicopathological factors

The relationships between recurrence-free survival and other clinicopathological parameters of periampullary carcinoma with unequivocal epicenter are summarized in Table 7.

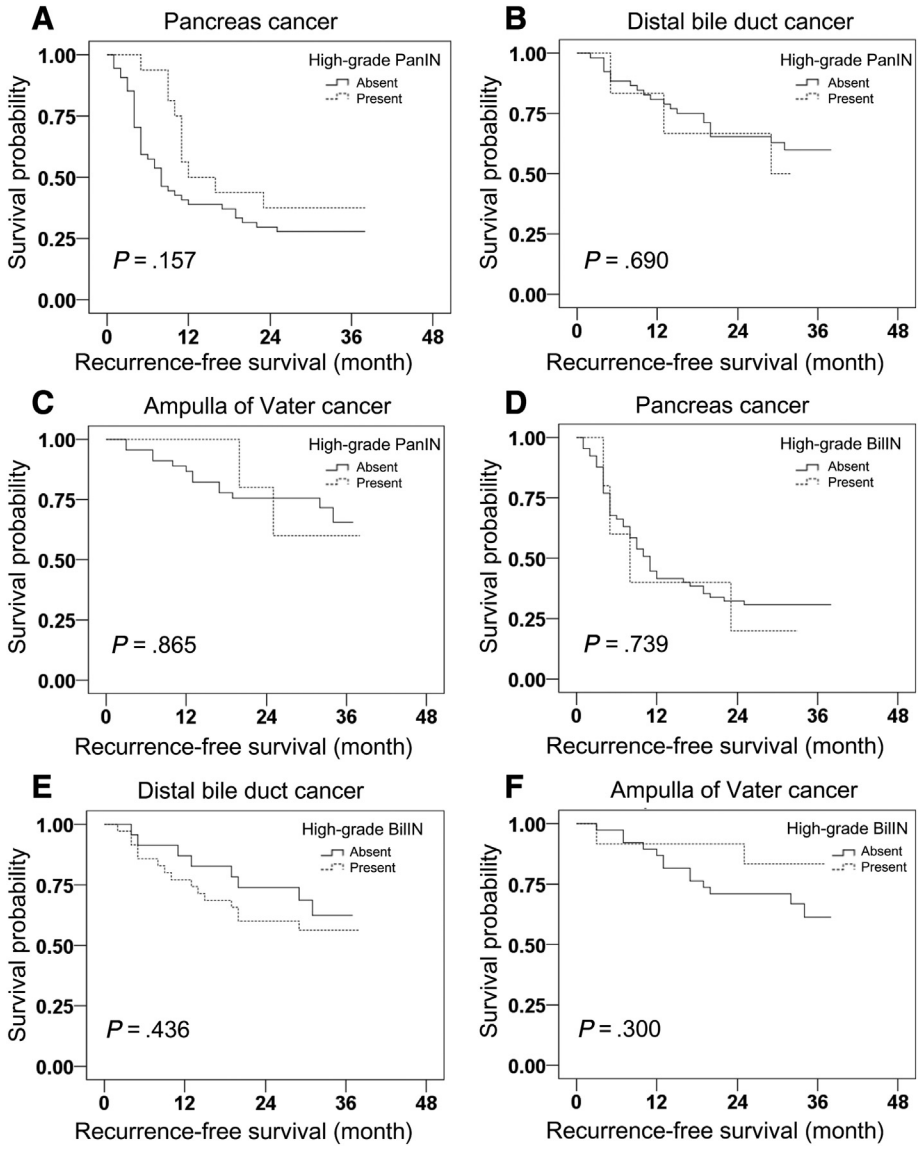


**Fig. 4** Recurrence-free survival comparison based on the presence of high-grade PanIN or BilIN among patients with periampullary cancers. No significant recurrence-free survival was observed based on the status of high-grade PanINs in pancreatic cancer (A; medians, 12 months for patients with high-grade PanIN and 8 months for those without high-grade PanIN; $P = .157$), distal bile duct cancer (B; medians, 28 months for patients with high-grade PanIN and 29 months for those without high-grade PanIN; $P = .690$), and ampulla of Vater cancer (C; medians, 31 months for patients with high-grade PanIN and 36 months for those without high-grade PanIN; $P = .865$). No significant recurrence-free survival was observed based on the status of high-grade BilINs in pancreatic cancer (D; medians, 8 months for patients with high-grade BilIN and 11 months for those without high-grade BilIN; $P = .739$), distal bile duct cancer (E; medians, 28 months for patients with high-grade BilIN and 30 months for those without high-grade BilIN; $P = .436$), and ampulla of Vater cancer (F; medians, 31 months for patients with high-grade BilIN and 31 months for those without high-grade BilIN; $P = .300$).

The pancreatic origin ($P < .001$), larger tumor size ($P = .032$), presence of perineural invasion ($P < .001$), lymphovascular invasion ($P < .001$), lymph node metastasis ($P < .001$), and poorly differentiated tumors ($P = .001$) were significantly associated with worse recurrence-free survival. In contrast, the presence of high-grade PanINs or high-grade BilINs was not statistically associated with recurrence-free survival.

### 3.8. Multivariate analyses of clinicopathological factors

The Cox proportional hazard model was used with other significant clinicopathological factors to determine their prognostic significance for recurrence-free survival. On multivariate analysis, pancreas origin ($P = .004$), the presence of

lymph node metastasis ($P < .001$), perineural invasion ($P = .025$), and poorly differentiated tumors ($P = .027$) were independent worse prognostic factors (Table 7).

## 4. Discussion

The location of the tumor epicenter (either mucosal or serosal portion) and the presence of peritumoral dysplasias are frequently used to differentiate primary cancers from secondary malignancies of the gastrointestinal tracts [20,21]. We adopted this concept to identify the location of 368 primary periampullary carcinomas, including periampullary carcinomas with 256 unequivocal and 112 clinically equivocal epicenter. The key findings of the present study are as follows: (1) PanINs were more common in cancers of the pancreas and the ampulla of Vater; (2) BilINs were more common in cancers of the distal bile duct and the ampulla of Vater; (3) high-grade PanINs were more common in pancreatic cancers; and (4) high-grade BilINs were more common in distal bile duct cancers. These findings were expected owing to the biologic relationships between the intraepithelial precursor lesions and the infiltrating cancers. Both precursor lesions show the accumulation of genetic alterations as the morphologic grades of dysplasia increase, and they demonstrate identical genetic alterations in the infiltrating cancers. Therefore, the presence of these lesions could be suggestive of the origin of the adjacent invasive carcinoma.

Deshpande and colleagues [18] demonstrated that features suggestive of distal bile duct cancer are symmetric (or concentric) bile duct involvement and the presence of high-grade BilINs (BilIN-2 or BilIN-3). On the other hand, features suggestive of pancreatic cancer are asymmetrical bile duct involvement, the presence of high-grade PanINs (PanIN-2 or PanIN-3), and more *KRAS* mutation [18]. Our results were concordant with those of the earlier study by Deshpande et al. High-grade PanINs (PanIN-3) were more common in pancreatic cancers, whereas high-grade BilINs (BilIN-3) were more common in distal bile duct cancers in this study. The difference between the present and previous studies is that we considered only BilIN-3 as a high-grade BilIN and PanIN-3 as a high-grade PanIN. However, Deshpande et al considered both PanIN-2 and PanIN-3 as high-grade PanINs and included both moderate bile duct dysplasia (BilIN-2) and severe bile duct dysplasia (BilIN-3) as high-grade BilINs. Regardless of the cutoff used for the definition of high-grade intraepithelial lesions, the important fact is that high-grade BilINs are more common in cancers of the distal common bile duct, whereas high-grade PanINs are more frequent in pancreatic cancers. Furthermore, the present study revealed that presence of intraepithelial lesions has an important meaning for identifying the exact origin of periampullary cancers with the ROC curve analyses in both periampullary carcinomas with 256 unequivocal and 112 clinically equivocal epicenters. We also evaluated the status of PanINs, including high-grade PanINs, and BilINs, including high-grade BilINs, in other periampullary carcinomas, such as ampulla of Vater and duodenal cancers. Although PanINs and BilINs were also frequently noted in ampulla of Vater cancers, high-grade PanINs and high-grade BilINs were uncommonly observed. In contrast, none of BilINs or PanINs were identified in duodenal cancers.

Based on gross patterns and the involvement of the ampulla and surrounding anatomic structures, Adsay et al [6] classified ampullary carcinomas into the following types: intra-ampullary papillary tubular neoplasm associated, periampullary duodenal, ampullary-ductal, and ampullary not otherwise specified. They demonstrated those distinct clinicopathological patterns in relation to each type of ampullary cancer. Briefly, the intra-ampullary papillary tubular neoplasm–associated type had minimal involvement of the duodenal surface and had the best prognosis; the ampullary-ductal type demonstrated the smallest tumor size but had the worst prognosis; and the periampullary duodenal type had an exophytic or ulcerofungating growth pattern, demonstrated the largest tumor size, was most commonly associated with lymph node metastasis and the eccentric involvement of the ampulla, and had an intermediate prognosis [6]. They demonstrated that patients with ampullary carcinoma had better survival rates than did those with pancreatic cancers [6]. No significant difference in survival was shown between patients with duodenal cancer and those with ampullary cancer of the periampullary duodenal type [6]. Interestingly, no high-grade PanINs or high-grade BilINs were seen in duodenal cancers in the present study, whereas low-grade BilINs and low-grade PanINs were noted commonly in ampullary cancers. By combining the information on the epicenter of tumors (duodenum versus ampulla of Vater) and on the status of BilINs or PanINs, discriminating between the epicenter of duodenal versus ampullary carcinomas may be made easier in daily pathology practice.

Identifying the precise location of periampullary carcinomas is important for several reasons. First, patients with pancreatic ductal adenocarcinomas usually have worse survival rates than do those with other periampullary carcinomas [22,23]. The results of our present study demonstrate that patients with pancreatic ductal adenocarcinomas had worse recurrence-free survival than did those with other periampullary carcinomas, including carcinomas of the distal bile duct, the ampulla of Vater, and the duodenum. These results were concordant with the findings of previous studies [6,18,23]. Second, recommended follow-up schedules are different based on the epicenter of the periampullary cancers. Patients with pancreatic cancer are recommended to have follow-up visits every 3 to 6 months after surgical resection [24]. In contrast, patients with distal bile duct cancers are recommended to visit every 3 months during the first 2 years and attend 6-month visits afterward [25]. Patients with ampullary and duodenal cancer did not have specific guidelines for surveillance after the surgical resection of their tumors, probably because of the low incidence of these tumor types. Finally, chemotherapeutic regimens for adjuvant therapy are different based on the epicenter of the periampullary cancer. Doublet regimens of gemcitabine and capecitabine are preferred in the adjuvant chemotherapy of pancreatic cancers [26], whereas multiple

chemotherapeutic options are considered in the case of recurrent or metastatic disease [24,26]. Concurrent chemoradiotherapy with 5-fluorouracil or capecitabine is often prescribed for patients with distal common bile duct cancer, whereas gemcitabine-cisplatin combination chemotherapy is the first-line therapy for locally advanced or metastatic disease [25]. There is no consensus regarding the optimal treatment options for ampullary and duodenal cancers, but chemotherapy regimens for colorectal adenocarcinoma, such as 5FU or capecitabine, might be helpful in duodenal adenocarcinomas [27]. The evaluation of BilINs and PanINs in the distal bile duct and pancreatic parenchyma can therefore help identify the epicenter of periampullary cancers for the above-mentioned reasons.

Several attempts have been made to identify the specific location of periampullary cancers based on histologic type (pancreatobiliary type, intestinal-type, etc) [22,28-30]. Pancreatobiliary-type adenocarcinomas show simple or branching glands with a single layer of low columnar epithelial cells without nuclear pseudostratification and are surrounded by abundant desmoplastic stroma [31]. In contrast, intestinal-type tumors have cribriform glands consisting of tall, pseudostratified columnar cells similar to those seen in adenocarcinomas of the colon [31]. Survival rates of patients with periampullary cancer with the intestinal histologic type were better than those of patients with the pancreatobiliary type [22,32]. Interestingly, the intestinal histologic subtype showed better prognostic significance, whereas the tumor origin could not predict the prognosis [22]. However, these histologic subtypes could not specify the origin of periampullary cancers. For example, intestinal-type cancers are reported in pancreatic ductal adenocarcinoma cases [33]. Therefore, based on our observations, determining the origin of the tumor depends on the anatomic location as well as the investigation of intraepithelial precursor lesions.

Interestingly, BilINs were reported more commonly in lower pT categories of periampullary cancers, whereas PanINs were observed more frequently in higher pT categories. These results may show that higher pT categories (pT3-pT4) are more common in pancreatic cancer (113/114 cases; 99.1%). In contrast, lower pT categories (pT1-pT2) were seen more often in other periampullary cancers (distal bile duct [32/82 cases; 39.0%] and ampulla of Vater [34/54 cases; 63.0%]) in the present study. The more frequent occurrence of lower T categories in cancers of the bile duct or of ampullary origin than in pancreatic cancers can be explained by the wide regional spread of pancreatic ductal adenocarcinomas and the earlier detection of distal common bile duct or ampullary cancers due to symptoms caused by biliary obstruction [34,35].

In the present study, we evaluated the status of PanINs and/or BilINs both in 256 periampullary carcinomas with unequivocal epicenters (test set) and in 112 periampullary carcinomas with clinically equivocal epicenters (validation set) and observed that high-grade BilINs were more common in cancers of the distal common bile duct, whereas high-grade PanINs were more frequent in pancreatic cancers both in periampullary carcinomas with unequivocal epicenters (test set) and in clinically equivocal epicenters (validation set). Therefore, presence of high-grade PanINs or high-grade BilIN can be used for evaluation of exact origin of periampullary carcinomas, especially when they showed equivocal location either by imaging or by endoscopic finding, based on our observation.

The present study has several limitations. First, because of the inclusion of consecutively resected cases, the number of duodenal cancers was smaller than that of other periampullary cancers. Second, all the examined cases were from a single institution; therefore, further multi-institutional studies are required. Despite these limitations, to the best of our knowledge, our study is the first to demonstrate an association between high-grade intraepithelial lesions and the origin of the tumor in all 4 periampullary cancer types.

Identification of the exact origin of periampullary cancers may also be carried out based on small endoscopic biopsies acquired from the endoscopic retrograde cholangiopancreatography examination of the peritumoral distal common bile duct and the endoscopic ultrasound-guided fine needle aspiration biopsy of the peritumoral pancreas. Further studies with small biopsies of the distal common bile duct as well as the pancreatic parenchyma acquired by endoscopic retrograde cholangiopancreatography and endoscopic ultrasound-guided fine needle aspiration biopsy are required. In addition, their usefulness in surgically resected specimens should be emphasized because they may facilitate the application of these procedures in daily practice. The identification of high-grade PanINs or BilINs is based on histologic appearance using routine hematoxylin and eosin staining and does not require any additional process such as immunohistochemical staining or molecular studies [11,15]. The only measure that pathologists are required to take is a careful examination of the surrounding nontumorous pancreatic parenchyma and the biliary epithelium of the distal common bile duct to identify any precursor lesions.

In summary, high-grade PanINs are seen most commonly in pancreatic cancers, whereas high-grade BilINs are observed most frequently in distal common bile duct cancers. In addition, both high-grade PanINs and high-grade BilINs are uncommonly noted in ampullary or duodenal cancers. Recognition of high-grade intraepithelial lesions will help identify the primary origin of periampullary cancers in the future, especially when the epicenter of the periampullary cancer is ambiguous.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2018.09.006.

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