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MINIREVIEWS

Intraductal papillary neoplasm of the bile duct: The new frontier of biliary pathology

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Abstract

Intraductal papillary neoplasms of the bile duct (IPNBs) represent a rare variant of biliary tumors characterized by a papillary growth within the bile duct lumen. Since their first description in 2001, several classifications have been proposed, mainly based on histopathological, radiological and clinical features, although no specific guidelines addressing their management have been developed. Bile duct neoplasms generally develop through a multistep process, involving different precursor pathways, ranging from the initial lesion, detectable only microscopically, *i.e.* biliary intraepithelial neoplasia, to the distinctive grades of IPNB until the final stage represented by invasive cholangiocarcinoma. Complex and advanced investigations, mainly relying on magnetic resonance imaging (MRI) and cholangioscopy, are required to reach a correct diagnosis and to define an adequate bile duct mapping, which supports proper treatment. The recently introduced subclassifications of types 1 and 2 highlight the histopathological and clinical aspects of IPNB, as well as their natural evolution with a particular focus on prognosis and survival. Aggressive surgical resection, including hepatectomy, pancreaticoduodenectomy or both, represents the treatment of choice, yielding optimal results in terms of survival, although several endoscopic approaches have been described. IPNBs are newly recognized preinvasive neoplasms of the bile duct with high malignant potential. The novel subclassification of types 1 and 2 defines the histological and clinical aspects, prognosis and survival. Diagnosis is mainly based on MRI and cholangioscopy. Surgical resection represents the mainstay of treatment, although endoscopic resection is currently applied to nonsurgically fit patients. New frontiers in genetic research have identified the processes underlying the carcinogenesis of IPNB, to identify targeted therapies.

Key Words: Intraductal neoplasm of the bile duct; Bile duct neoplasms; Cholangiocarcinoma; Intraductal papilloma; Classification; Treatment

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Core Tip: Intraductal papillary neoplasms of the bile duct are rare premalignant lesions, which are especially prevalent in East Asia. Due to the lack of specific guidelines addressing their management, recent subclassification of types 1 and 2 clarifies several aspects, particularly histopathological, clinical and prognostic features. Magnetic resonance imaging and cholangioscopy occupy a central role in diagnosis and treatment. Surgery is the most appropriate treatment, yielding optimal results in terms of survival, although endoscopic techniques have been used, particularly in nonsurgically fit patients. Lastly, recent genetic research has focused on identifying targeted therapies acting on the stepwise progression of neoplastic biliary epithelium.

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INTRODUCTION

Intraductal papillary neoplasms of the bile duct (IPNBs), first described by Chen *et al*[1] in 2001, are a type of biliary tumors with a distinctive papillary growth inside the common bile duct lumen, and typically develop along the biliary tree. IPNBs are identified macroscopically, according to bile duct dilatation and intraductal masses apparent upon radiologic imaging[2-4]. Together with biliary intraepithelial neoplasia (BilIN)[5], IPNBs were first recognized as a premalignant lesion of invasive cholangiocarcinoma (CCA) in the 2010 World Health Organization (WHO) classification of tumors of the digestive system[6]. The term IPNB was introduced because of the similarities with intraductal papillary mucinous neoplasms (IPMNs) of the pancreas (IPMN-Ps). IPNBs are considered the biliary counterparts of IPMN-Ps[3,7,8], even though the simultaneous occurrence of both types is rare[9-19].

IPNBs are complex and generally require extensive multidisciplinary investigation. Accurate diagnosis of IPNB is mandatory to guide the therapeutic approach, with aggressive surgical resection being the treatment of choice, particularly in early stages. Endoscopic management has been described as a potential alternative in nonsurgically fit patients [20-24]. This review summarizes the current and latest concepts regarding IPNB, discusses the various morphological features of IPNB and its mimickers, and describes clinical approaches in the diagnosis and treatment that are useful for multidisciplinary management.

DEFINITION, EPIDEMIOLOGY AND CLINICAL FEATURES

Definition

Invasive bile duct neoplasms, *e.g.*, CCA[25], always develop through a multistep process, involving the two above-mentioned precursors: BilIN and IPNB[5]. While BilIN is a flat or low-papillary growth of dysplastic biliary epithelium, detected only microscopically, IPNB consists of an intraductal papillary growth of neoplastic biliary epithelium that can be identified macroscopically and is therefore visible on imaging[3,5].

BilINs have been classified into three grades described as mild, moderate and severe dysplasia, or as low-grade dysplasia, high-grade dysplasia and carcinoma *in situ*[26]. Recently, several cytological features, namely detailed cellular and nuclear changes, glandular involvement, mitosis, nuclear location and intraepithelial neutrophils, have been incorporated into the categorization of BilINs, allowing the identification of three histological grades: BilIN-1, BilIN-2 and BilIN-3 (including the so-called carcinoma *in situ*)[26].

IPNBs are typically represented by a papillary or villous tumor growing inside the bile duct lumen and composed of papillary stalks with fine vascular cores that can develop anywhere along the biliary tree, involving both the intrahepatic and extrahepatic bile ducts[2-4]. Although already described in 2001[1], the term IPNB was introduced by the revised WHO Classification of Tumors of the Digestive System in 2010[6], incorporating different entities; for example, the previously named mucin-producing CCA, papillary CCA (PCC), mucin-hypersecreting bile duct tumor, IPMN of the bile duct, biliary papilloma or papillomatosis, papillary adenocarcinoma of the bile duct, and intraductal growth type CCA[5,6].

Epidemiology, risk factors and clinical features

IPNB is an uncommon disease, with a prevalence of 5%-15% among bile duct tumors and mainly reported in series from East Asia[22,27-30]. It is reported in relation to specific and common risk factors identified such as hepatolithiasis and

liver parasitic infections (*Clonorchis sinensis* and *Opistorchis viverrini*)[2,4]. Other series described the association of IPNB with hepatocellular carcinoma[31], primary sclerosing cholangitis[32] and mixed adenoneuroendocrine carcinoma[33]. Conversely, IPNBs have been described only in isolated reports from Europe, with a propensity of a more invasive course and an extrahepatic location in comparison to those reported in eastern centers[5,34-36]. Similarly, previous reports describing the association of IPNBs with IPMN-Ps are sporadic, as summarized in Table 1[9-19].

IPNB tends to be more frequent in men aged > 65 years, presenting clinically with right upper abdominal discomfort/pain, jaundice, and cholangitis. It has been demonstrated that 5%-29% of patients might be asymptomatic[2,37]. Elevation of total and direct bilirubin, alkaline phosphatase, -glutamyl transferase, alanine aminotransferase and aspartate aminotransferase are common laboratory findings. Increased levels of tumor markers, *i.e.* carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9, have been documented in approximately 25% and 40% of patients, respectively[37].

Although the mucin produced by IPNBs is usually retained inside the neoplastic cells, in up to one-third of cases, elevated quantities of mucin are secreted into the bile duct lumen, leading to intermittent obstruction of the bile flow with consequent upstream and downstream duct dilatation[5]. This particular type of IPNB has been named by some authors as IPMNs of the bile duct[5].

HISTOLOGIC AND MACROSCOPIC FEATURES

Histologic aspects

No precise criteria for grading the biliary epithelium dysplasia within IPNBs have been established. Some authors have divided IPNBs into four types based on the worsening degree of dysplasia, ranging from type 1, low grade, to type 4, stromal invasion of adenocarcinoma[2,5]. Others have classified IPNBs into noninvasive and invasive lesions, including adenoma, borderline tumor, and carcinoma *in situ* in the first group and tubular or mucinous adenocarcinoma in the other group[30,37]. Invasive carcinomas arising from IPNBs have been described in 30%-75% of cases, according to the different surgical series, with a 9%-15% rate of lymph node metastasis at the time of surgical resection[2,27-29,38] and an overall better prognosis when compared to normal CCA[2,21,22,28,39].

Anatomical location and geographical distribution of IPNBs have been correlated with the risk of stromal invasion. Stromal invasion is higher in tumors originating in the extrahepatic bile ducts, and in those affecting Caucasian patients, suggesting a more indolent course of intrahepatic IPNBs (I-IPNBs) and in those occurring in Asian countries[2,3,28,38,40]. Nakanuma *et al*[41] recently reviewed the pathological features of invasive carcinoma associated with IPNB, identifying three different patterns of increasing invasiveness, A, B and C. The first showed a favorable postoperative overall survival (OS) similar to that of noninvasive types, in contrast to the latter two that might be considered clinically advanced entities.

The neoplastic epithelia of IPNB is categorized into four histological phenotypes according to hematoxylin and eosin staining: pancreatobiliary (PB), intestinal, gastric and oncocytic[3,4,42] (Figure 1). The PB type consists of columnar or cuboidal cells with eosinophilic cytoplasm, round hyperchromatic nuclei and scarce mucinous appearance. This variant is usually immunohistochemically positive for mucin (MUC)1, MUC5AC, cytokeratin (CK)7 and S100P[3,4,42]. The intestinal type resembles a colorectal villous neoplasm, showing columnar cells with cigar-shaped nuclei, basophilic cytoplasm, and variable amount of sopranuclear mucin. Immunohistochemically, the cells express MUC2 and MUC5AC but not MUC1[3,4,42]. The gastric type features the gastric foveolar epithelium, consisting of tall columnar cells with basally oriented nuclei and abundant cytoplasmic mucin, generally associated with pyloric glands. While the latter are typically positive for MUC6, the foveolar portions frequently express MUC5AC and CK7 but rarely MUC1 and MUC2[3,4,42]. The oncocytic type presents with convoluted and branching papillae lined by one or different layers of cuboidal/columnar cells with hyperchromatic, round and large nuclei, and abundant, intensely eosinophilic cytoplasm, consistently expressing MUC5AC and focally MUC1 and/or MUC2[3,4,42].

The PB and intestinal patterns are the most common and usually associated with invasive lesions. The remaining two histological types are uncommon and generally present with an indolent course[3,4,42] (Figure 2).

Macroscopic and radiological aspects

Four morphological subtypes have been recognized based on the gross pathological picture: polypoid, superficial-spreading, cystic, and cast-like[5,42]. The polypoid type describes an intraductal lesion, pedunculated or sessile, sometimes reaching great dimensions. Differential diagnosis involves typical CCA and bile duct stones when tumor pieces disintegrate inside the bile ducts[5,42].

The superficial spreading type depicts a tumor barely visible on imaging that spreads along varying lengths of the bile ducts. Radiologically, it appears as isolated bile duct dilatation without an obvious obstructing lesion, secondary to copious mucin production by the tumor. Any biliary obstruction leading to bile duct dilatation can mimic this form, although a real stricture cannot generally be identified in this variant of IPNB[5,42].

The cystic type develops as a focal cystic dilatation of a bile duct that maintains the communication with the lumen of the adjacent bile duct, thus configuring the pattern of a pseudocyst. This feature allows differentiation of the cystic type IPNB from the mucinous cystic neoplasms, *i.e.* cystadenomas and cystadenocarcinomas, where in the absence of a luminal communication, mucin secretion is confined within the neoplastic cyst. In addition, the presence of ovarian-like stroma is necessary to diagnose mucinous cystic neoplasms[5,42]. Lastly, mural nodules or mucin aggregates are common findings in this form of IPNB[5].

Table 1 Summary of reported synchronous intraductal papillary neoplasms of the bile duct and pancreas

Refs	Age (yr)	Sex	IPNB			IPMN-P			Treatment
			Site	Size (cm)	Histology	Site	Size (cm)	Histology	
Joo *et al*[9]	60	M	LL	1.5 × 1.5	Benign	T	2.5 × 2.5	Benign	LH + SPDP
Ishida *et al*[10]	67	M	S1	4 × 3	Benign	UP	3.5 × 3	Benign	LH + S1 segmentectomy + resection of uncinate process
Yamaguchi *et al*[11]	69	M	S2-3	6.5 × 3.5	Malignant	H	3 × 2.5	Malignant	S2-3 segmentectomy + PPPD
Zalinski *et al*[12]	65	F	LL	10 × 10	Malignant	H	NR	High-grade dysplasia	NR
Park *et al*[13]	67	M	S2-3	NR	Medium-grade dysplasia	T	2.5 × 1	Medium-grade dysplasia	S2-3 segmentectomy + DP + splenectomy
Xu *et al*[14]	68	F	S2-3	5 × 4	Benign	T	0.5:1	Benign	laparoscopic S2-3 segmentectomy + SPDP
Valente *et al*[15]	76	F	CBD + LHD + RHD	2.5 × 1.8	Malignant	UP + T	1:1.3	Malignant	CHT + RT
Ren *et al*[16]	52	M	Distal CBD	NR	Malignant	EP	NR	Benign	PPTP
Luvira *et al*[17]	53	M	CBD + LHD + RHD	NR	Malignant	EP	NR	Low-grade dysplasia	L trisectionectomy + PPTP + splenectomy
Moon *et al*[18]	66	F	LL	NR	Malignant	EP	NR	Malignant	LH + TP + splenectomy
Tarantino *et al*[19]	55	F	CBD	NR	NR	H	11	Malignant	NR

IPNB: Intraductal papillary neoplasm of the bile duct; IPMN-P: Intraductal papillary mucinous neoplasm-pancreatic; M: Male; F: Female; LL: Left lobe; T: Tail; LH: Left hepatectomy; SPDP: Spleen preserving distal pancreatectomy; EP: Entire pancreas; UP: Uncinate process; H: Head; PPPD: Pylorus preserving pancreaticoduodenectomy; NR: Not reported; DP: Distal pancreatectomy; CBD: Common bile duct; LHD: Left hepatic duct; RHD: Right hepatic duct; CHT: Chemotherapy; RT: Radiotherapy; PPTP: Pylorus preserving total pancreatectomy; TP: Total pancreatectomy.

In the cast-like type, the tumor occupies the lumen of the bile duct, expanding along the longitudinal axis. Although radiologically it appears as a cast-like lesion, histologically it presents as a polyp, with only a small attachment to the biliary epithelium[5,42].

This macroscopic classification presents some common elements with the classification of mucin-producing CCA proposed by Sakamoto *et al*[43] in 1997, which included the duct-ectatic, cystic and intermediate types. In the first group, papillary tumors developed within diffusely dilated intrahepatic ducts. In the second, large cystic lesions with papillary projections were found inside the liver, communicating with intrahepatic bile ducts. In the latter pattern, large cystic lesions were intermingled with solid tumors invading the liver parenchyma[43]. Histologically, all the CCAs were papillary adenocarcinoma, demonstrating a superficial spread along the bile duct mucosa in almost half of the cases[43].

CLASSIFICATIONS

Recently, Kim *et al*[44] resumed the duct-ectatic and cystic subgroups of I-IPNBs that together accounted for most tumors in their surgical series (68.5%), while the remaining were extrahepatic (26.6%) and diffuse (4.1%) types. The latter included lesions diffusely affecting both the intrahepatic and extrahepatic bile ducts. In this modified anatomical classification, as named by the authors, no significant difference in terms of OS was recorded among the three groups[44].

Another radiological-pathological classification was introduced by Luvira *et al*[45] in 2017. Five different categories of IPNB were described in their series of 103 patients: (1) Classical I-IPNB with an intraductal tumor determining unilateral duct dilatation; (2) extrahepatic IPNB (E-IPNB) with an intraductal tumor producing bilateral intrahepatic duct dilatation; (3) cystic lesion with a papillary tumor inside, communicating with the lumen of the bile duct; (4) micropapillary tumor causing disproportionate bile duct dilatation without a clear lesion radiologically evident; and (5) mass-forming tumor with macroinvasion[45]. Their analysis concluded that the category of IPNB and the presence of lymph node metastasis represented the only significant prognostic factors, with class II and V showing worse OS[45].

Novel subclassification of types 1 and 2 IPNBs

In 2020, the Japan Biliary Association and the Korean Association of Hepato-Biliary-Pancreatic Surgery, after retro-

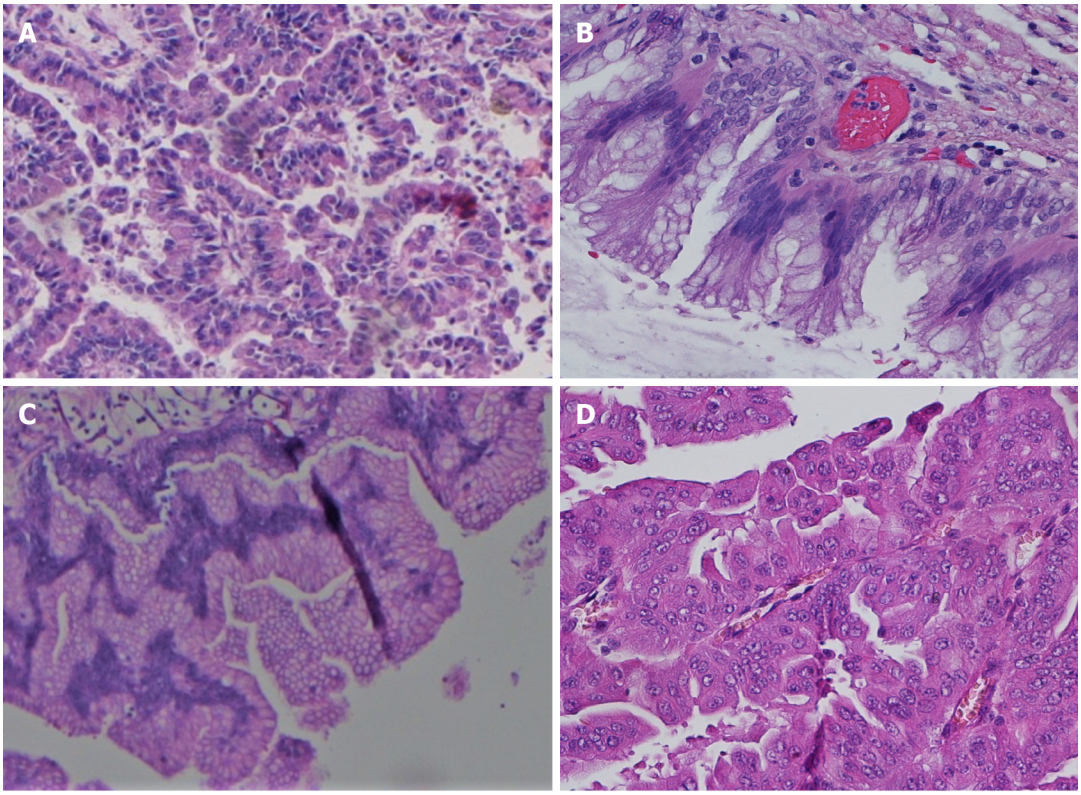

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Figure 1 Histological subtypes of intraductal papillary neoplasms of the bile duct. A: Pancreatobiliary; B: Intestinal; C: Gastric; D: Oncocytic. Hematoxylin and eosin staining.

spectively reviewing the clinicopathological data of 694 patients who had undergone surgery for IPNB over a 20-year period, proposed new histopathological diagnostic criteria and identified types 1 and 2 IPNB[28]. Type 1 showed a regular growth with papillary, villous or tubular homogenous structures, thin papillary fibrovascular stalks and a large amount of mucin, and type 2 displayed a heterogenous appearance and an irregular growth with complicated structures, such as cribriform, compact tubular, solid or large cystic components and rare mucin overproduction[28] (Figure 3). In addition, associated invasive carcinoma was reported in almost all cases of type 2 lesions (93.6%), while low-intermediate- or high-grade dysplasia was observed in 9.7% and 40.2% of type 1 lesions, respectively, with ~50% of these exhibiting stromal invasion[28]. The intestinal and gastric histological subtypes were generally associated with type 1, while incidence of the PB subtype was significantly higher in the second group[28].

Clinically, type 1, representing the majority (75%) of tumors reviewed in that multicenter analysis, tended to be more frequent at the level of intrahepatic bile ducts. Conversely, the type 2 tended to develop inside the extrahepatic ducts leading to significantly higher levels of bilirubin, alkaline phosphatase, -glutamyl transferase, alanine aminotransferase, aspartate aminotransferase and tumor markers (CEA and CA19-9), with increased occurrences of liver dysfunction, jaundice and pain[28].

Radiologically, type 1 IPNB typically presented with the aspects of extensive cystic duct dilatation or intraductal cauliflower-like lesion, whereas an intraductal solid mass determining upstream duct dilatation was the classic pattern of type 2[46]. The above-mentioned study highlighted that bile duct margin status after surgical resection did not affect OS and disease-free survival (DFS) in both groups, and there was no significant difference in recurrence rate (RR) observed between types 1 and 2, although lymph node metastasis rate was significantly higher in type 2[28]. Nevertheless, patients with type 2 IPNBs had significantly lower OS and DFS at 1, 3 and 5 years when compared to those with type 1 IPNBs, leading the authors to conclude that their new classification might be strongly predictive of the patient outcome[28].

Although the above-mentioned binary classification was included in the most recent WHO classification of digestive system tumors[47], the differential diagnosis between these two types of IPNBs has been challenging, particularly in the hands of unexperienced pathologists. Accordingly, Onoe *et al*[30] developed a scoring system based on six pathological features aimed at differentiating between type 1 and 2 IPNBs. Lesions scoring a total of 5 or 6 were categorized as type 1, whereas those scoring 0 or 1 and 2-4 were categorized as type 2 or unclassifiable, respectively. The authors confirmed the findings of a prevalent intrahepatic location of type 1 IPNB in comparison to the extrahepatic site for type 2, and the survival rates were higher in the first group compared to type 2 or unclassifiable lesions[30].

As other authors have suggested[2,46], type 1 IPNBs might be considered the real biliary counterpart of IPMN-Ps, particularly the main duct variant, while type 2 might be identified as PCC, indicating that papillary bile duct tumors occupy a single continuous spectrum, ranging from less advanced forms, *i.e.* type 1, to more advanced forms, *i.e.* type unclassifiable and type 2. The geographic distribution is divergent between types 1 and 2, with the former being predominant in Asia and the latter in Europe and the USA[46,48].

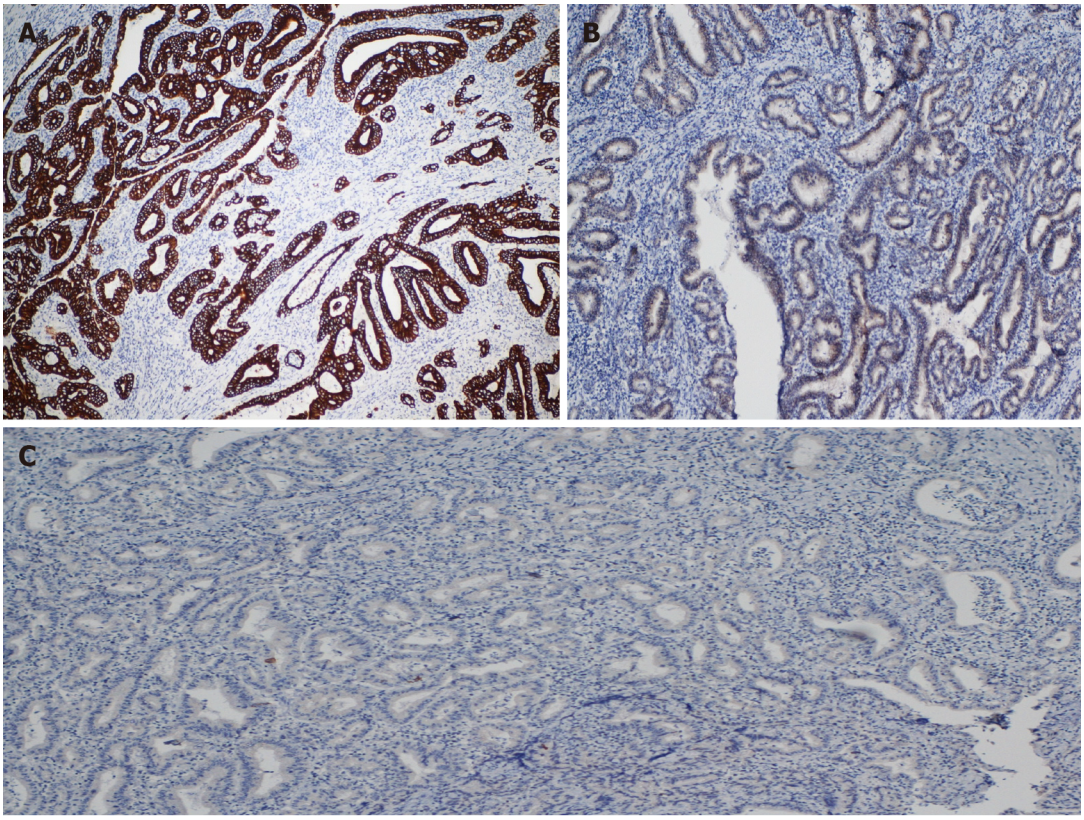

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Figure 2 Histological features of intraductal papillary neoplasms of the bile duct with irregular growth pattern and foci of invasive carcinoma (pancreatobiliary type). A: Immunostaining positive for cytokeratin (CK)19; B: Immunostaining negative for CDX2; C: Immunostaining negative for CK20.

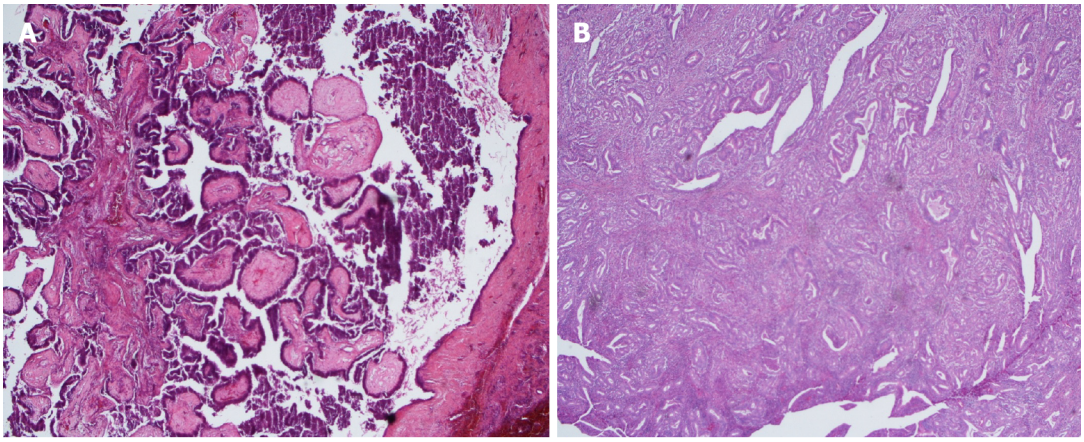

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Figure 3 Subclassification of intraductal papillary neoplasms of the bile duct according to the Japan Biliary Association and the Korean Association of Hepato-Biliary-Pancreatic Surgery. A: Type 1 consists of papillary, villous or tubular homogenous structures with thin papillary fibrovascular stalks; B: Type 2 consists of thick papillary glands with irregular branching, often intermingled with solid irregular components. Hematoxylin and eosin staining.

DIAGNOSIS: CROSS-SECTIONAL IMAGING, ENDOSCOPY AND CHOLANGIOSCOPY

Routine diagnostic methods used in IPNBs are represented by computed tomography (CT) and magnetic resonance imaging (MRI), commonly showing intraductal masses associated with bile duct dilatation[42]. On CT, IPNBs generally present an enhancement pattern of isointensity or hyperintensity during the late arterial phase with an occasional intense rim enhancement at the base of the lesions. On MRI, IPNBs tend to be hypointense on T1-weighted images and hyperintense on T2-weighted images, which has the advantage of identifying small intraductal or multiple tumors[2,4,37] (Figure 4).

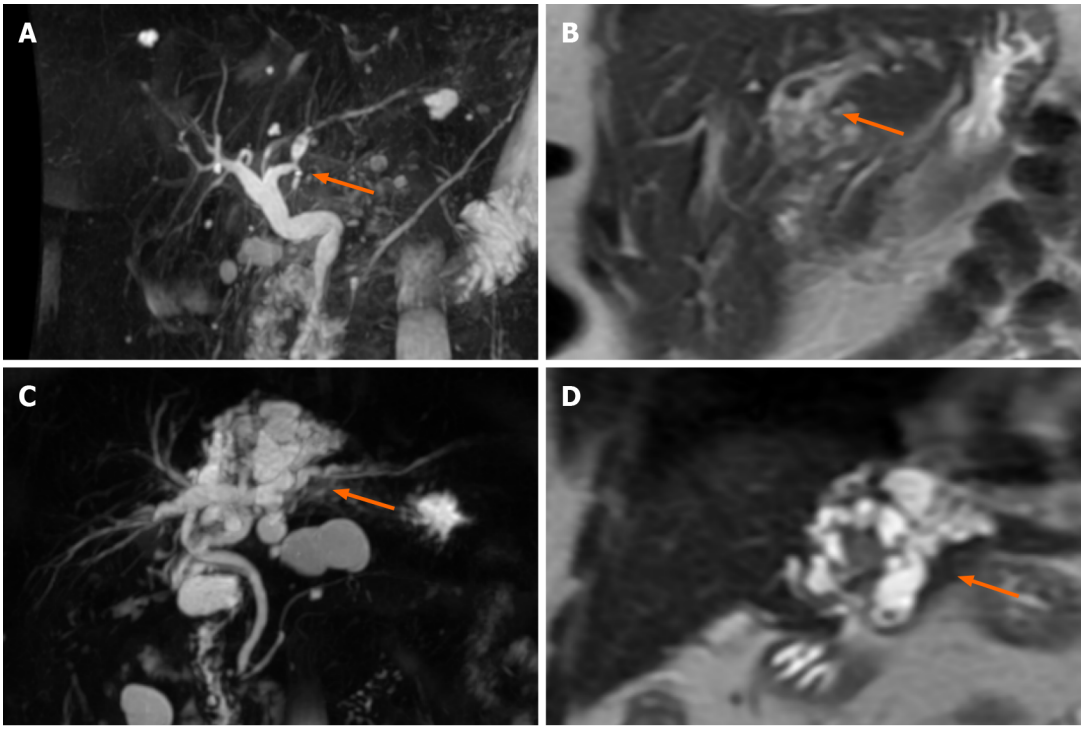

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Figure 4 Magnetic resonance imaging of intraductal papillary neoplasms of the bile duct. A: Magnetic resonance cholangiopancreatography showed an intraductal lesion of the left hepatic duct with upstream bile duct dilatation; B: Diffuse dilatation of the intrahepatic left lobe bile ducts with low intensity tumors (T2 weighted image, coronal section); C: Magnetic resonance cholangiopancreatography showed a cystic type intraductal papillary neoplasm of the bile duct; D: Cystic type intraductal papillary neoplasm of the bile duct (T2 weighted image, coronal section).

Lee *et al*[20] recognized significant features on MRI that are useful in differentiating IPNBs with an associated invasive carcinoma from noninvasive forms. They included an intraductal visible mass, tumor size ≥ 2.5 cm, tumor multiplicity, adjacent organ invasion, and bile duct wall thickening. Bile duct wall thickening had the highest diagnostic accuracy. However, the superficial spread and progression of IPNBs along the bile duct mucosa might be underestimated by conventional imaging[21]. For this reason, intraductal ultrasonography and direct cholangioscopy play a central role in assessing these parameters; that is, the depth and extent of invasion, and in performing a biopsy of the lesion[2,21].

Nevertheless, the discrepancy between the preoperative biopsy and the definitive histology after surgical resection might be notable, particularly in E-IPNB, with a reported negative predictive value of ~40%. This means that ~60% of patients with a preoperative diagnosis of nonmalignancy actually have an invasive carcinoma by definitive pathology [40]. Since these two methods have been widely applied in the evaluation of IPNBs, the current applications of endoscopic retrograde cholangiography are limited, apart from determining the presence of mucobilia or direct communication between a cystic lesion and the bile duct[4] (Figure 5). Therefore, classifications of IPNBs based on their cholangiographic patterns, such as the one proposed by Yeh *et al*[49], no longer have a significant clinical utilization.

High-risk stigmata of malignancy

Few studies have focused on the analysis of features that might anticipate the risk of invasiveness and/or malignant degeneration in IPNBs[29,40]. In a recent large surgical series, the presence of CEA > 5 IU/mL, CA19-9 > 37 IU/L, a mural nodule > 12 mm, intrahepatic calculi and lymph node enlargement were identified as potential predictors of malignancy in I-IPNB, while total bilirubin > 3 mg/dL, enhancement of mural nodules and CA19-9 > 37 IU/L were potential risk factors in E-IPNB[40].

However, after multivariate analysis, mural nodule > 12 mm [relative risk (RR): 5.33, 95% confidence interval (CI): 1.05-26.89, P = 0.043] and the enhancement of mural nodules (RR: 19.08, 95% CI: 1.08-335.5, P = 0.044) were confirmed as the only significant predictors of malignancy in I-IPNB and E-IPNB, respectively[40]. These two features were identified as absolute surgical indications in IPMN-Ps, according to the 2018 European Guidelines and the 2017 International Consensus Guidelines[50,51].

TREATMENT

Based on the remarkable frequency of high-grade dysplasia or invasive carcinoma and of symptoms reported in IPNBs and on the poor sensitivity of preoperative biopsy, particularly in invasive forms, treatment should be considered mandatory, with surgery representing the main therapeutic option[21].

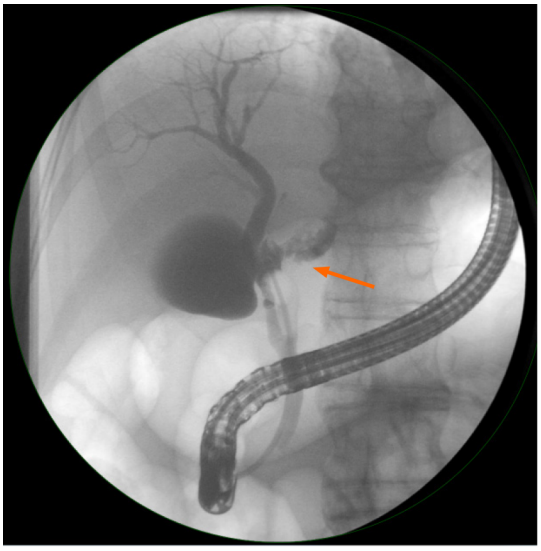

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Figure 5 Endoscopic retrograde cholangiopancreatography of an intrahepatic intraductal papillary neoplasm of the bile duct showed a direct communication between the cystic lesion and the bile duct.

Surgical resection

The type and extent of surgical resection depends on the location of the IPNB, with bile duct resection or pancreaticoduodenectomy applied to E-IPNB and hepatic resection to I-IPNB. Regional lymphadenectomy should always be carried out since the incidence of regional lymph node metastasis is estimated to be 9%-15%[2,27-29].

R0 resection has been reportedly achieved in 90% of patients[4], and the presence of residual disease, including dysplasia, in the resection margin should indicate further resection, although specific guidelines are not available[21]. According to Uemura *et al*[52] and Luvira *et al*[53], only the bile duct margin positive for carcinoma represented a significant poor prognostic factor. Jung *et al*[54] reported the presence of any dysplasia, even if low, in the bile duct margin as having a significant impact on OS and DFS to the same extent as carcinoma *in situ* or invasive carcinoma. Similarly, Youn *et al*[29] identified R1 resection (although, not specifying any dysplasia or carcinoma) as the most important factor for poor outcome in terms of OS and RR, together with high serum levels of CA19-9 (> 37 IU/mL). Conversely, Kubota *et al*[28] in a large surgical series, found that the status of the surgical margin (positive *vs* negative) did not influence the OS, DFS or RR in types 1 and 2 IPNBs, indicating that this parameter does not affect the prognosis.

Role of liver transplantation

Liver transplantation might be considered the only definitive and curative treatment in patients with extensive superficial spread along the bile duct mucosa, bilobar disease or with positive surgical margins, even after multiple resections. However, only limited experience has been described in the literature so far[55-58].

Other therapeutic approaches

In nonsurgically fit patients, some palliative treatments, such as percutaneous transhepatic biliary drainage, biliary stenting and endoscopic approaches (including cholangioscopic electrocoagulation, submucosal resection, argon plasma coagulation, radiofrequency ablation, and transpapillary intraluminal radiotherapy), have been reported[24,59-61].

Among the endoscopic treatments described, the IPNB lesion can be resected *via* electrocoagulation using a high-frequency electric needle knife that directly targets and destroys the tumor tissue[61], through either the classical method of submucosal resection by using polypectomy snares[23], the argon plasma coagulation method that dehydrates the tissue by blocking the blood flow into the lesion and dries the surrounding area[59,62,63], or the radiofrequency ablation method that induces coagulative necrosis of the neoplastic tissue[24]. In particular, the advantage of electrocoagulation relies on its concomitant utilization with cholangioscopy[61], with the ability to reach intrahepatic lesions, which is different from the other techniques that are used by classical endoscopy. Alternatively, transpapillary intraluminal radiotherapy with a high dose of iridium-192 can be delivered directly into the lesion by using an ultrathin flexible probe. Response to treatment can be easily monitored through conventional imaging, and sessions can be repeated according to treatment response[60].

PROGNOSIS AND SURVIVAL

Few reports exist in the literature investigating the natural evolution of untreated IPNBs. In the series of 196 patients with IPNBs by Han *et al*[40], only 16 (9 I-IPNB and 7 E-IPNB) did not undergo surgery and were observed during a median period of ~3 years. Of those with intrahepatic lesions, 55.5% experienced a malignant transformation *versus* 28.5% of those

belonging to the other group. In addition, 33.3% were admitted due to cholangitis *versus* 57.0% of the patients with E-IPNB. The remaining patients did not develop either malignancy or any type of symptoms related to their IPNBs.

Although survival data have varied widely among different series, the studies generally agree on the concept of a significantly improved OS and DFS for surgically resected IPNBs compared to conventional CCAs, with associated decreased rates of lymph node and distant metastases[2,22,36,37,39]. Several factors have been reported to be significant predictors of outcome after surgical resection of IPNBs, although most of them have not been well established or are still considered controversial[27,28,39,44,52].

For example, Rocha *et al*[7] reported depth of invasion (≥ 5 mm, < 5 mm, or none) and percentage of invasive carcinoma components (≥ 10%, < 10%, or none) as the main significant prognostic factors, with patient OS inversely proportional to the grade of invasion and to the proportion of malignancy detected in the IPNB. Similarly, Onoe *et al*[64] investigated 184 patients with PCCs and documented the presence of > 50% invasive components, defined as PCC-4, as an independent predictor of survival that approached the 5-year OS of patients with non-PCCs. The authors concluded that, although IPNBs might be nosologically applied only for PCC cases with < 50% invasive component, their prognostic classification of PCCs according to the proportion of invasive components indicated that all subgroups belonged to a singular disease group[64].

The classification of IPNBs into types 1 and 2, according to their clinical and histopathological features, has been generally recognized as a significant predictor of survival[27,28,52], independent from the grade of dysplasia and/or presence of invasive carcinoma. The 1-, 3-, 5- and 10-year OS rates for type 1 IPNB were 96.1%, 85.2%, 75.2% and 58.5%, respectively, and for type 2 IPNB were 94.6%, 69.1%, 50.9% and 26.8%, respectively ($P < 0.0001$). The 1-, 3-, 5- and 10-year DFS rates for type 1 were 88.3%, 73.8%, 64.1%, and 52.2%, respectively, and for type 2 IPNB were 81.0%, 48.0%, 35.3% and 25.8%, respectively ($P < 0.0001$)[28].

For all these features, type 1 IPNB might be considered the real biliary counterpart of IPMN-Ps, while PCCs might be included in the subgroup of type 2 IPNB, as stated above[2,46]. Likewise, Matsumoto *et al*[38] identified I-IPNB as those with more regular histopathological characteristics and favorable prognosis similar to type 1 in comparison with E-IPNB that might resemble type 2. Another significant poor prognostic factor recognized in several studies was lymph node metastasis, which carried an increased risk of locoregional recurrence[27,28,44,52,53]. Controversial results in terms of prognosis and survival have emerged from the analysis of other distinctive features of IPNBs, such as macroscopic appearance, histological subtype, immunohistochemical phenotype, and level of CA19-9[27,28,39,52,53].

IPNB GENETIC CHANGES AND TARGETED THERAPIES: THE NEW FRONTIERS

Recent genetic analyses of IPNBs have identified several mutations involving different oncogenes and oncosuppressor genes, such as *KRAS*, *BRAF*, *GNAS*, *RNF43*, *TP53*, *APC*, *CTNNB1*, *ZNRF3*, *CDKNZA* and *SMAD4*. The altered expression is strictly related to the different immunohistochemical patterns observed[65-68]. Accordingly, at least three main signaling pathways have been identified in the carcinogenesis of IPNBs: RAS-MAPK, controlled by the *KRAS* and *BRAF* oncogenes; WNT-β-catenin, regulated by the oncogene *CTNNB1* and by two oncosuppressor genes, *APC* and *ZNRF43*; and GPCR-CAMP, activated by mutations of the oncogene *GNAS*[65-68].

In particular, since mutations affecting the *APC* and *CTNNB1* genes have been rarely detected in IPMN-Ps, the WNT-β-catenin pathway appears to have a unique role in the molecular alterations underlying the neoplastic transformation of the biliary epithelium, acting in the early phases of carcinogenesis. Dysregulation of other signaling pathways, particularly the RAS-MAPK pathway, has been described in different neoplasms, such as colorectal, pancreatic and lung cancers[65-68]. In addition, *KRAS* and *GNAS* mutations were frequently identified in type 1 IPNB, often of the intestinal subtype, which share several clinicopathological features with IPMN-Ps, while mutations in the *APC* oncosuppressor gene and in the *CTNNB1* oncogene, that is, the WNT-β-catenin pathway, were generally described in type 2, often associated with the PB subtype[65-68].

These genetic studies confirmed that IPNBs consist of at least two distinct entities, and that the type 1 and 2 subclassifications, recently introduced by the Japan Biliary Association and the Korean Association of Hepato-Biliary-Pancreatic Surgery, may reflect these genetic subcategorizations[65-68]. For all these reasons, recent research has focused its attention on these dysregulated signaling pathways, especially the WNT-β-catenin pathway, identifying several target agents that are currently under evaluation in clinical trials and preclinical studies of application to solid and hematological neoplasms[69,70]. Recently, preliminary valuable results have emerged from the NCT02675946 and NCT03507998 clinical trials evaluating the efficacy and safety of the WNT pathway porcupine inhibitor CGX1321 in advanced gastrointestinal neoplasms, including CCAs. However, at the time of this writing, none of these targeted therapies have been adopted in the field of IPNB management[71].

CONCLUSION

IPNBs are newly recognized preinvasive neoplasms of the bile duct with high malignant potential and a tendency to evolve to invasive CCAs. Although several classifications have been proposed over the past 10 years, the recently introduced subclassification of types 1 and 2 highlights the histopathological and clinical aspects of IPNBs, their natural evolution with a particular focus on prognosis, OS, DFS and similarities/discrepancies with IPMN-Ps. In relation to their complexity, advanced techniques used in a multimodal approach are needed for correct diagnosis and precise identification of their locations, extension and pathological extent.

Surgery with a radical intent represents the most appropriate treatment, although different methods, mainly consisting of endoscopic approaches, can be considered in nonsurgically fit patients. Genetic analysis of the specific mutations driving the stepwise progression of neoplastic biliary epithelium might represent an innovative research field in terms of targeted therapies, particularly those implicating the WNT-β-catenin pathway.

FOOTNOTES

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