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LETTER TO THE EDITOR

Current considerations on intraductal papillary neoplasms of the bile duct and pancreatic duct

Efstathios T Pavlidis, Ioannis N Galanis, Theodoros E Pavlidis

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Abstract

Pancreatobiliary intraductal papillary neoplasms (IPNs) represent precursors of pancreatic cancer or bile duct cholangiocarcinoma that can be detected and treated. Despite advances in diagnostic methods, identifying these premalignant lesions is still challenging for treatment providers. Modern imaging, biomarkers and molecular tests for genomic alterations can be used for diagnosis and follow-up. Surgical intervention in combination with new chemotherapeutic agents is considered the optimal treatment for malignant cases. The balance between the risk of malignancy and any risk of resection guides management policy; therefore, treatment should be individualized based on a meticulous preoperative assessment of high-risk stigmata. IPN of the bile duct is more aggressive; thus, early diagnosis and surgery are crucial. The conservative management of low-risk pancreatic branch-duct lesions is safe and effective.

Key Words: Biliary tree diseases; Pancreatic cystic neoplasms; Biliary tract neoplasms; Extrahepatic cholangiocarcinoma; Pancreatic adenocarcinoma

Core Tip: The balance between overlooking a potential malignancy and the outcomes of a high-risk major operation should be accounted for in the decision-making process of the therapeutic plan. Despite the use of modern diagnostic modalities, overtreatment may occur in many patients; thus, the correct management of pancreatobiliary intraductal papillary neoplasms (IPNs) must be individualized. The proper management of pancreatobiliary IPNs is based on a precise preoperative diagnosis that correctly evaluates the defined high-risk stigmata and worrisome features.

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TO THE EDITOR

We read the paper by Mocchegiani *et al*[1] with great interest, and we would like to congratulate the authors for their very nice work on intraductal papillary neoplasm of the bile duct (IPNB), which is an updated impressive approach. This neoplasm resembles the pancreatic intraductal papillary mucinous neoplasm (IPMN). Taking this opportunity, we will make some considerable comments on pancreatobiliary intraductal papillary neoplasms since both IPNB and pancreatic IPMN have a common genomic background, corresponding manifestations and several similarities; however, peculiarities and some differences exist in their biological behavior and subsequent management. IPMN was first described by Ohashi *et al*[2] in 1982 as a different entity from mucinous cystic neoplasms and cancer and is considered a premalignant lesion of pancreatic ductal adenocarcinoma[3]. However, IPNB is rare, less common than IPMN, and more aggressive since it can progress to cholangiocarcinoma[4]. Both IPNB and IPMN are characterized by intraductal overproduction of mucin and growth of the papillary epithelium, which results in similar imaging findings[4].

Panceatobiliary intraductal neoplasms include: (1) IPMN pancreatic, IPNB; (2) Intraductal oncocytic papillary neoplasm (IOPN); and (3) Intraductal tubulopapillary neoplasm[5].

IBNB, first described by Chen *et al*[6] in 2001, is a slow-growing precancerous lesion that evolves into carcinoma[1,7,8]. The other precursor lesion of invasive cholangiocarcinoma, an aggressive disease with poor outcomes, is biliary intraepithelial neoplasia[7,9]. The mucin produced may cause transient ductal obstruction manifested by recurrent episodes of acute cholangitis, obstructive jaundice and bile duct dilatation[8,10]. IPNB must be considered when a patient presents with such a clinical situation without common bile duct gallstones. Early diagnosis and proper management of this precancerous lesion are important for preventing a dismal disease course and improving long-term oncological outcomes [4].

IPNB has histopathological features and genetic substrates, *i.e.*, gene mutations, similar to those of pancreatic IPMN. IPNB and IPMN usually constitute distinct entities with separate development. However, rare cases of simultaneous coexistence or even metachronic tract occurrences after initial surgical resection, which are rarer, have been reported[11]. Additionally, metachronic development of another new lesion may occur after curative intervention, but the development of a new lesion in the bile duct is less common than that in the pancreatic remnant[12].

The involved mutations included mutations in the *Tp16, TP53, KRAS, GNAS*, *BRAF*, SMAD4, STK11 *CTNNB1, PIK3CA, RNF43*, *APC*, *CTNNB1*, *ZNRF3*, *CDKNZA, BRCA 1* and *BRCA 2* genes[1,13,14]. There is an association between *KRAS* and *GNAS* gene mutations in IPNNs and between the *PRKACA* and *PRKACB* genes in IOPNs, which influences oncocytic tumorigenesis and morphology and may lead to therapeutic targets[13].

IPNB represents 5%-15% of relatively rare bile duct neoplasms and is found mainly in East Asia, particularly in elderly individuals older than 67 years[8,10,14,15]. These tumors develop throughout the intrahepatic (type 1) and extrahepatic (type 2) biliary tree[8,14]. Type 2 tumors are more common than type 1 tumors and have a worse prognosis. Magnetic resonance imaging (MRI)-magnetic resonance cholangiopancreatography (MRCP) features may be valuable in distinguishing between the two types of lesions and evaluating the risk of malignancy[15]. These tumors may be adenomas, borderline neoplasias, in situ carcinomas with regular overgrowth, or tubular mucinous adenocarcinomas with irregular overgrowth[1]. High peritumoral and intratumoral budding may be prognostic factors for worse outcomes in patients with extrahepatic distal cholangiocarcinoma[16].

Extensive radical surgical resection is the management method of choice for surgically fit patients with IPNB. Depending on the location, hepatectomy, pancreatoduodenectomy or radical common bile duct resection can be performed[10].

A recent European multicenter study showed a median postoperative survival of 5.7 years and a 5-year overall survival of 63%[17]. In unfit patients, novel endoscopic resection[1], endoscopic radiofrequency ablation or photodynamic therapy can be performed[8]. High-risk imaging findings and strong indications for surgery included a mural nodule more than 12 mm in length and mural nodule enhancement[1]. They are shown in Figure 1[1,4].

Pancreatic IPMNs represent approximately 1% of all pancreatic neoplasms and usually cause recurrent episodes of acute pancreatitis, which can lead to pancreatic dysfunction but may also be asymptomatic. The biological behavior of these tumors ranges from benign to malignant according to the type. The majority of these tumors do not progress to invasive pancreatic carcinoma. There are three types of lesions: Main-duct (MD)-IPMNs, branch-duct (BD)-IPMNs and mixed IPMNs[3]. Both age and metabolic syndrome increase the occurrence of IPMNs[18]. Acute pancreatitis predicts malignancy and constitutes an indication for pancreatectomy[19]. High-risk stigmata and worrisome features may predict malignant transformation in clinical practice and determine management policy, as shown in Table 1[3,20].

Improvements in diagnostic modalities have led to a continual increase in the incidence of IPNB[6]. MRI is the main imaging tool used[4,8,15]. These lesions are intraductal masses accompanied by proximal dilatation and occasionally distal dilatation. The "thread sign" shown in MRCP corresponds to filling defects due to mucin hypersecretion[4].

The first-line modern imaging techniques include contrast-enhanced ultrasound (US), MRI-MRCP and multidetector helical computed tomography, followed by endoscopic US (EUS)[8,21,22]. Additionally, EUS may provide guided needle biopsy[21].

Table 1 High-risk stigmata and worrisome features of malignant pancreatic intraductal papillary mucinous neoplasms

High-risk stigmata	Worrisome features
Dilated main pancreatic duct ≥ 10 mm	Cyst size 3 ≥ cm
Enhanced solid mural nodule 5 ≥ mm	Thickened and enhanced cyst wall
Obstructive jaundice	Abrupt dilatation of the main pancreatic duct 5-9 mm
	Distal atrophy of the pancreas
	Lymph node involvement

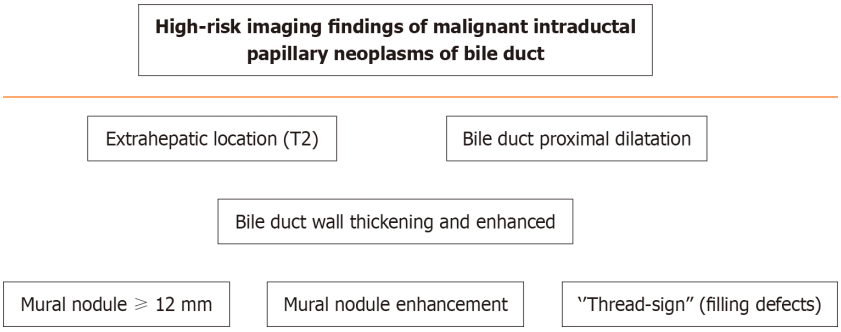

Figure 1 Scheme of Magnetic resonance imaging-cholangiopancreatography indications for malignant intraductal papillary neoplasm of the bile duct (bile duct).

Tumor metabolic activity was detected by positron emission tomography (PET) using ^{18}FDG-PET[8] or the novel ^{68}Ga-labeled fibroblast activation protein inhibitors-PET[23].

Peroral cholangioscopy[24] or pancreatoscopy[25] can directly visualize ducts to aid in diagnosing neoplastic lesions. Additionally, intraoperative pancreatoscopy[26] or even robotic pancreatectomy[27] can assist in determining the extent of pancreatectomy.

The serum elastase-1 concentration[28] and carbohydrate antigen 19-9 concentration or pancreatic juice cytology[29] may predict malignancy. Liquid biopsy may assist in determining malignancy by detecting cancer cells or molecular parts in the blood[30].

For the vast majority of MD-IPMNs and mixed IPMNs, surgery is needed. BD-IPMNs without high-risk stigmata have a low possibility of malignancy; thus, conservative management with long-term imaging surveillance is appropriate[31-34].

After curative resection, IPNB malignancies exhibit a better prognosis than original cholangiocarcinomas[8], and IPMNs exhibit a better prognosis than pancreatic ductal adenocarcinomas[35]; however, the recurrence rate is up to 27% for IPNB[15] and up to 43% for IPMN[36]. Thus, regular follow-up is mandatory for early recurrence detection and reoperation in the pancreatic remnant[37].

In conclusion, surgery is the cornerstone of management for patients at high risk for potential malignancies, particularly bile duct IPNB and pancreatic main duct IPMN. Long-term follow-up ensures early detection of recurrence. Conservative management and surveillance are indicated for patients with low-risk pancreatic branch duct IPMNs. However, management must be individualized to avoid overtreatment or overlooking a malignancy.

FOOTNOTES

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