The Pathologic and Genetic Characteristics of the Intestinal Subtype of Intraductal Papillary Neoplasms of the Bile Duct

病理科　　牛茜

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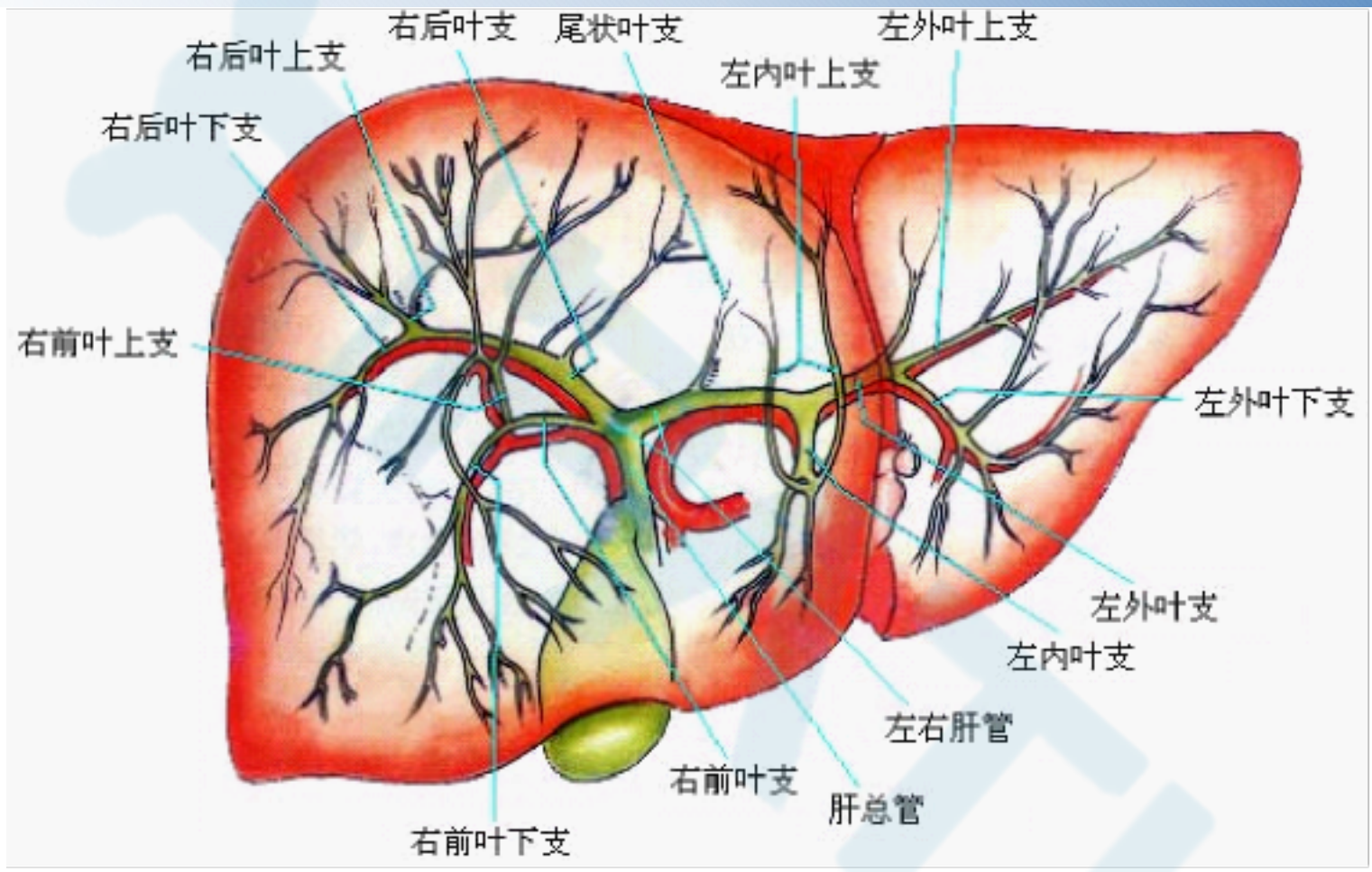
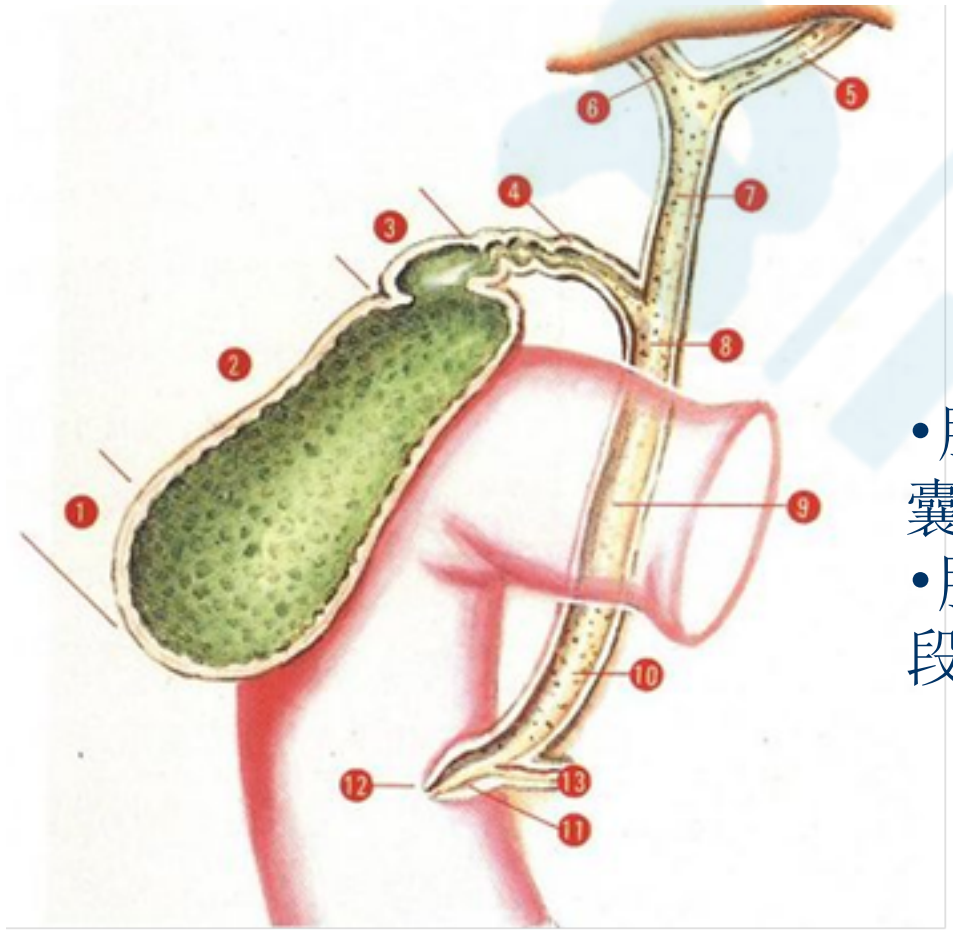
解剖基础



- 肝内胆管系统（肝胆管系统）
  - 包括毛细胆管、小叶间胆管、段间胆管、叶间胆管、肝内左右肝管
  - 左、右肝管为第一级分支
  - 左内叶、左外叶、右前叶、右后叶胆管为第二级分支
  - 各肝段胆管为第三级分支



•肝外胆管系统包括：肝外左、右肝管，肝总管，胆囊管，胆囊，胆总管。

•胆总管分4段：十二指肠上段、十二指肠后段、胰内段、十二指肠壁内段。

1 胆囊底　2 胆囊体　3 胆囊颈
4 胆囊管　5 左肝管　6 右肝管
7 肝总管　8 胆总管十二指肠上段
9 胆总管十二指肠后段　10 胆总管胰内段
11 胆总管十二指肠壁内段　12 十二指肠乳头
13 胰管

一、IPNB的流行病学特征和临床表现

- **IPNB**较为罕见，占胆道系统肿瘤的**4%~20%**，其病因不明，目前尚无完善的流行病学资料。**IPNB**在东亚国家高发，日本报道最多。
- 多数患者年龄为**50~70**岁，男性患者略多，男女比例为**(1.5~2.0)**:**1**。

- **IPNB**的临床表现比较特殊，反复发作的右季肋区疼痛和急性胆管炎，即间断性的黄疸和发热，传统胆管癌多表现为无痛性进行性黄疸。
- 该临床表现的原因可能是肿瘤质脆易于脱落，导致急性胆道梗阻；此外，分泌黏液的肿瘤亦可因黏液导致一过性的胆管梗阻。

二、IPNB的病理学特征

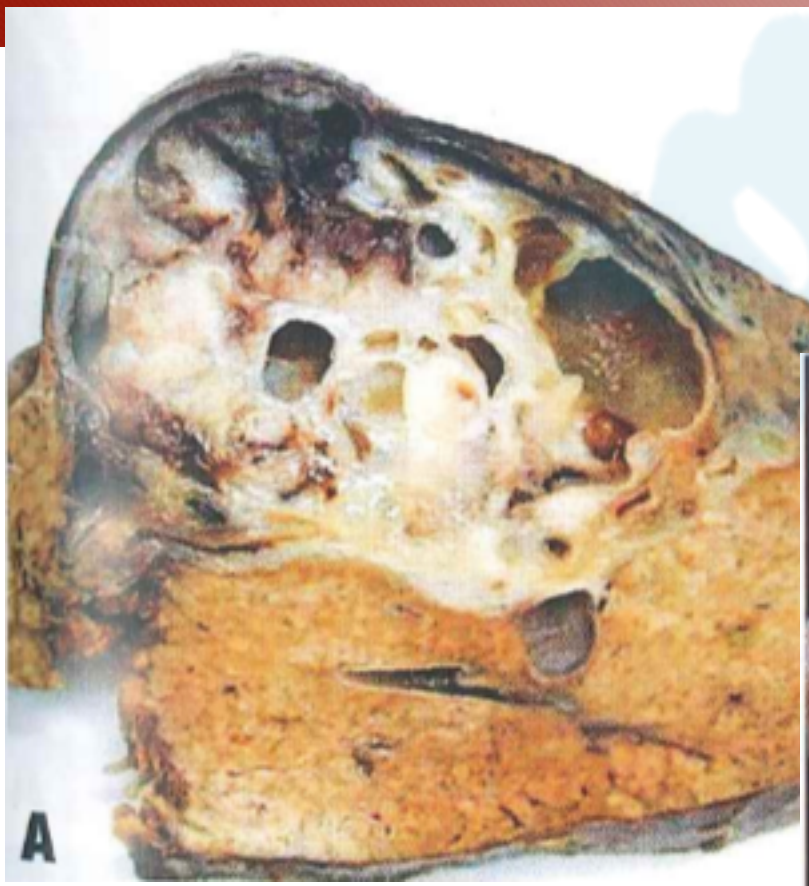
- **WHO**的定义将**IPNB**描述为：一种胆管上皮来源的外生型乳头状肿物，主要在胆管腔内生长，可发生于包括肝内胆管和肝外胆管的胆道系统任何部位，部分肿瘤具有分泌黏液的特性。

- **IPNB**的大体病理学特征表现

  单发或多发、

  灰色或黄色、

  质地脆性的乳头状肿物，绒毛状肿物；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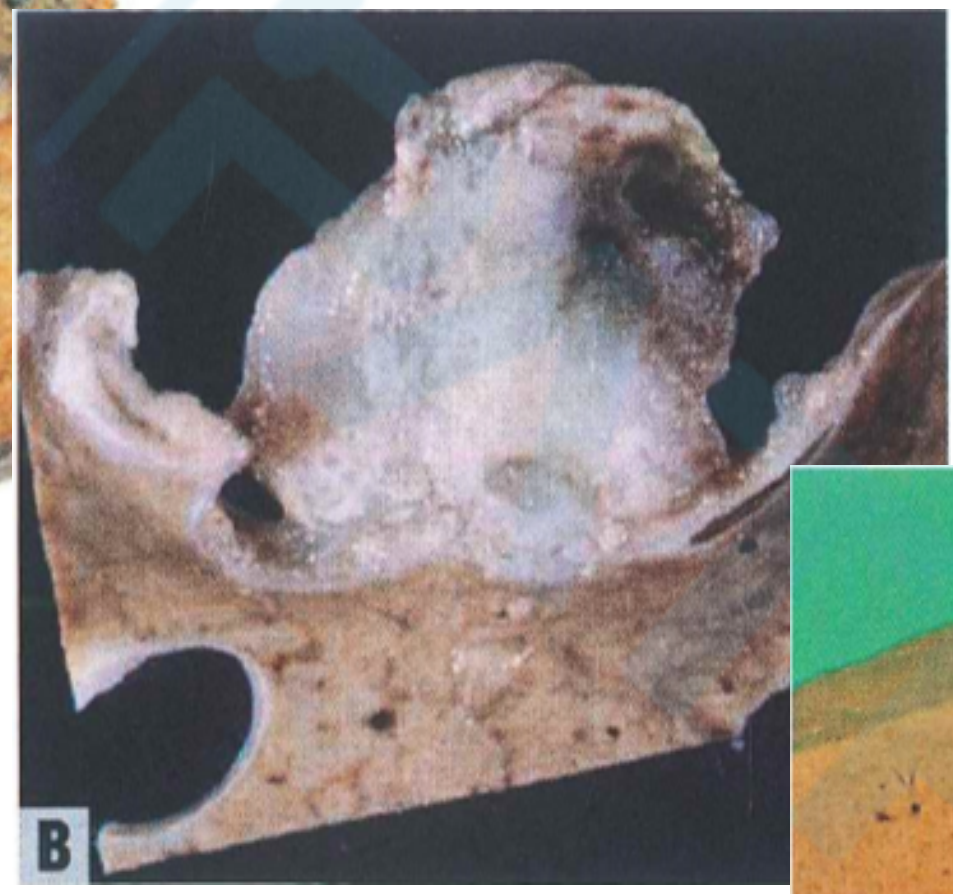
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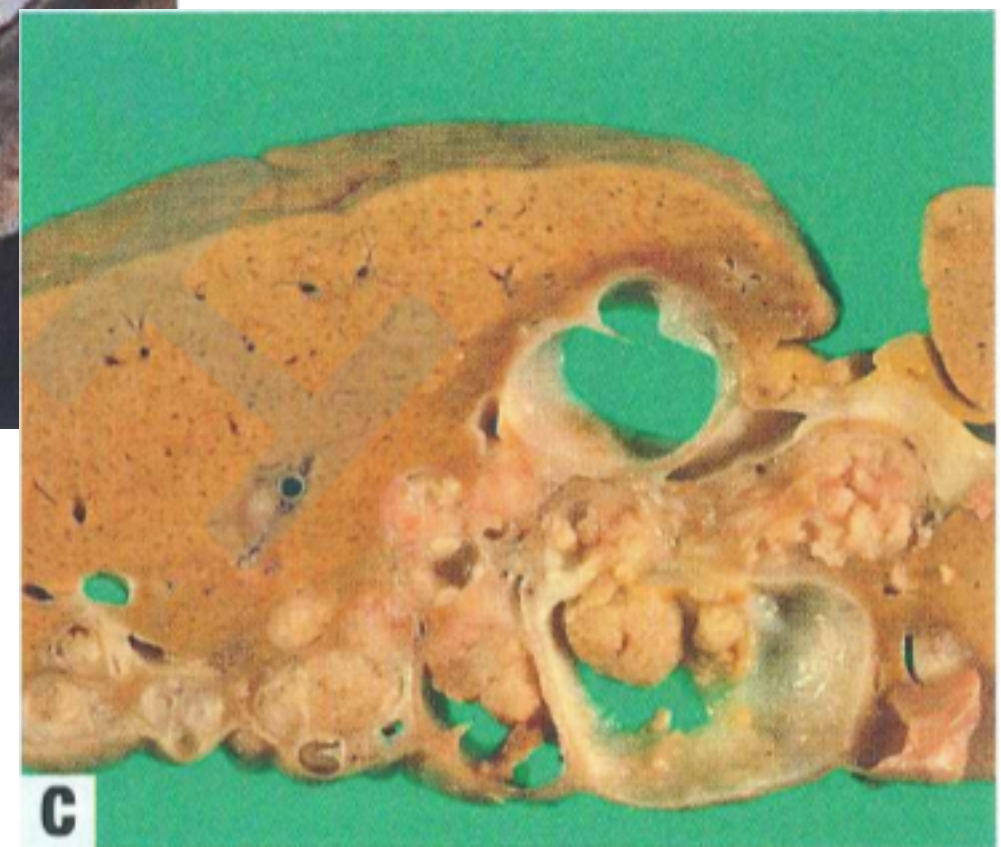
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镜下：胆管上皮细胞乳头样增殖，以蒂状结构与胆管壁相连，乳头轴心为纤维血管，可表现为腺瘤或腺癌。

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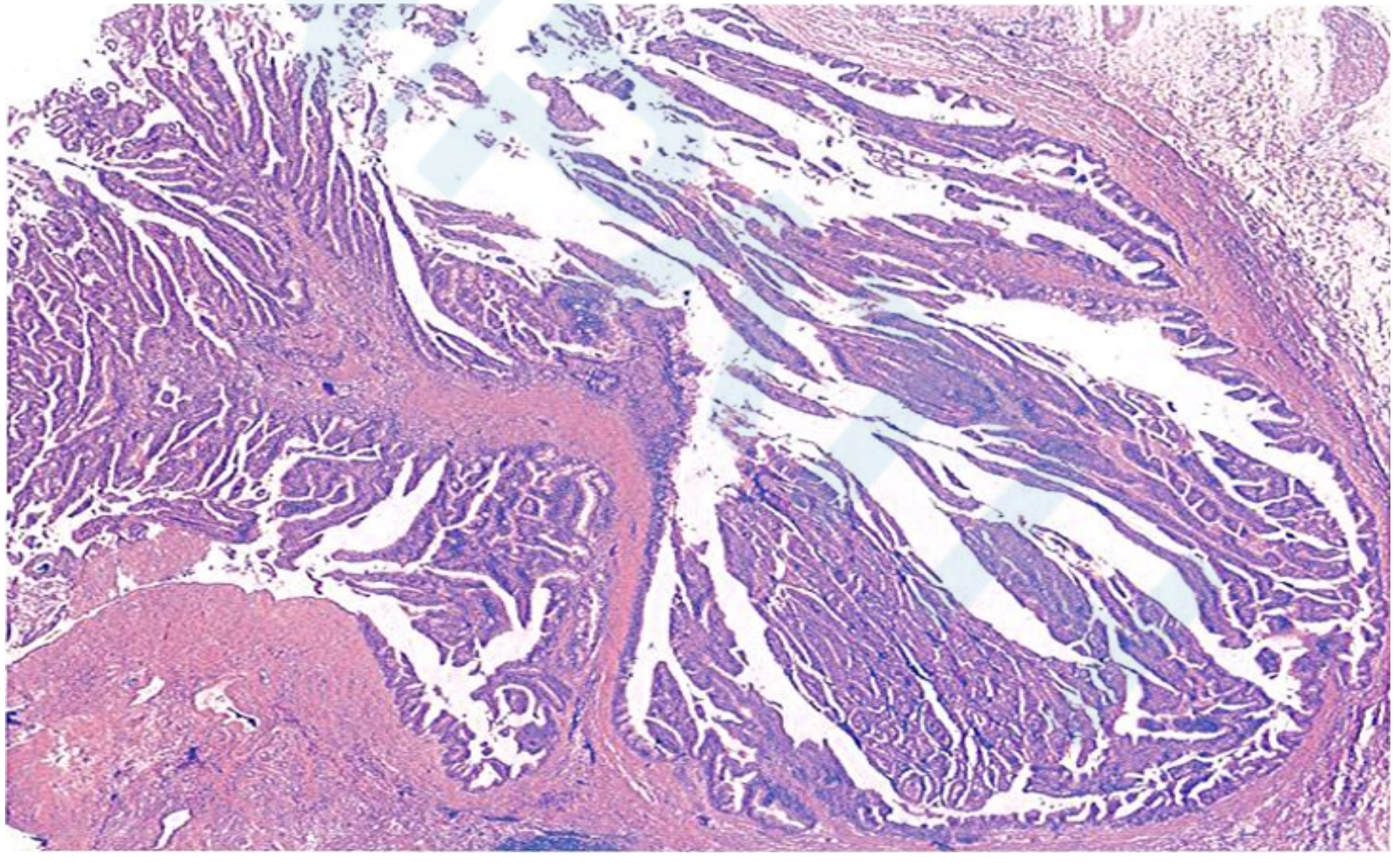
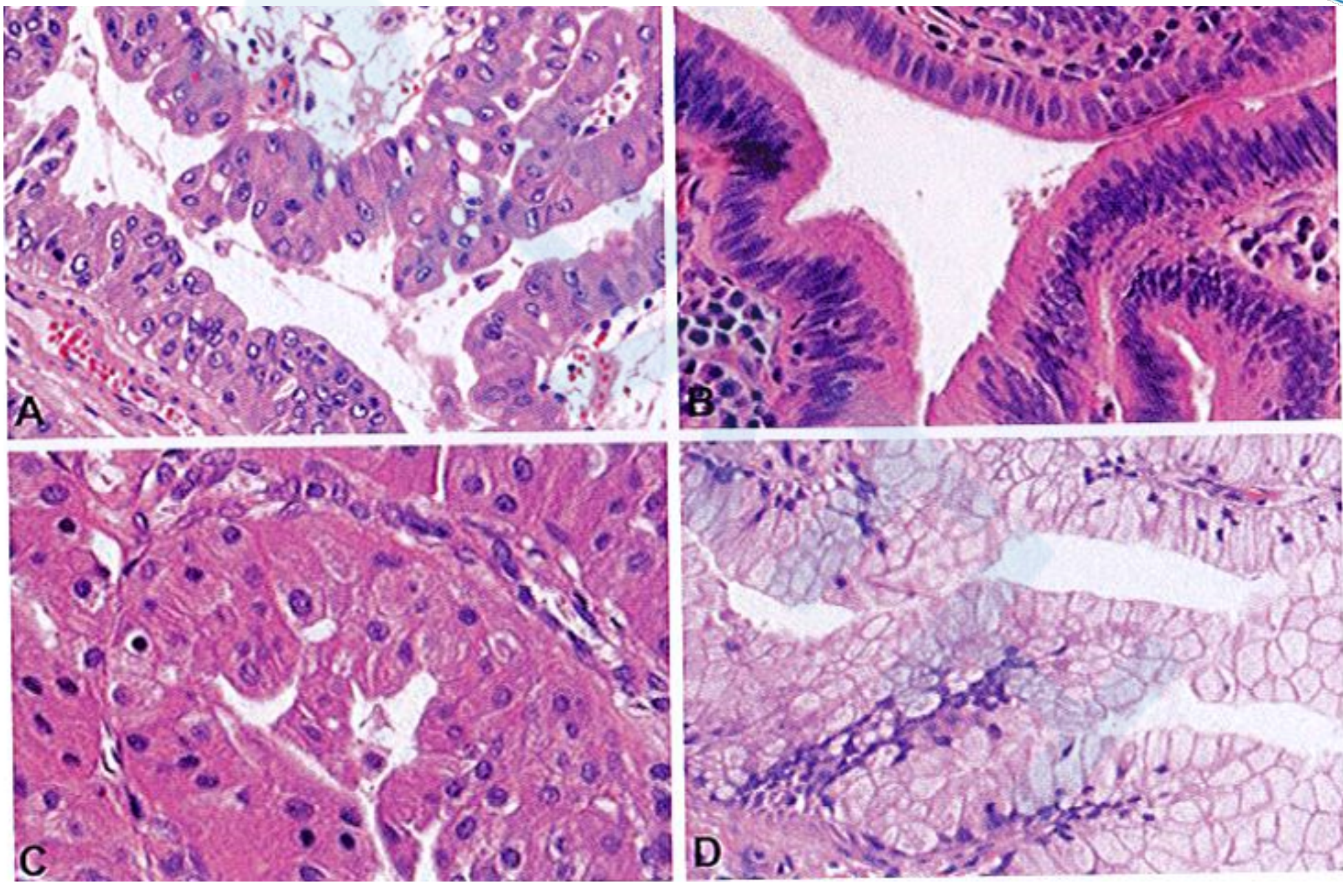


- **IPNB**在组织学上属于良性疾病。
- 约**35%**的**IPNB**患者在发病时或随访过程中出现恶性转化，因此被认为是一种癌前病变。
- **40%~80%**的**IPNB**内含有浸润癌。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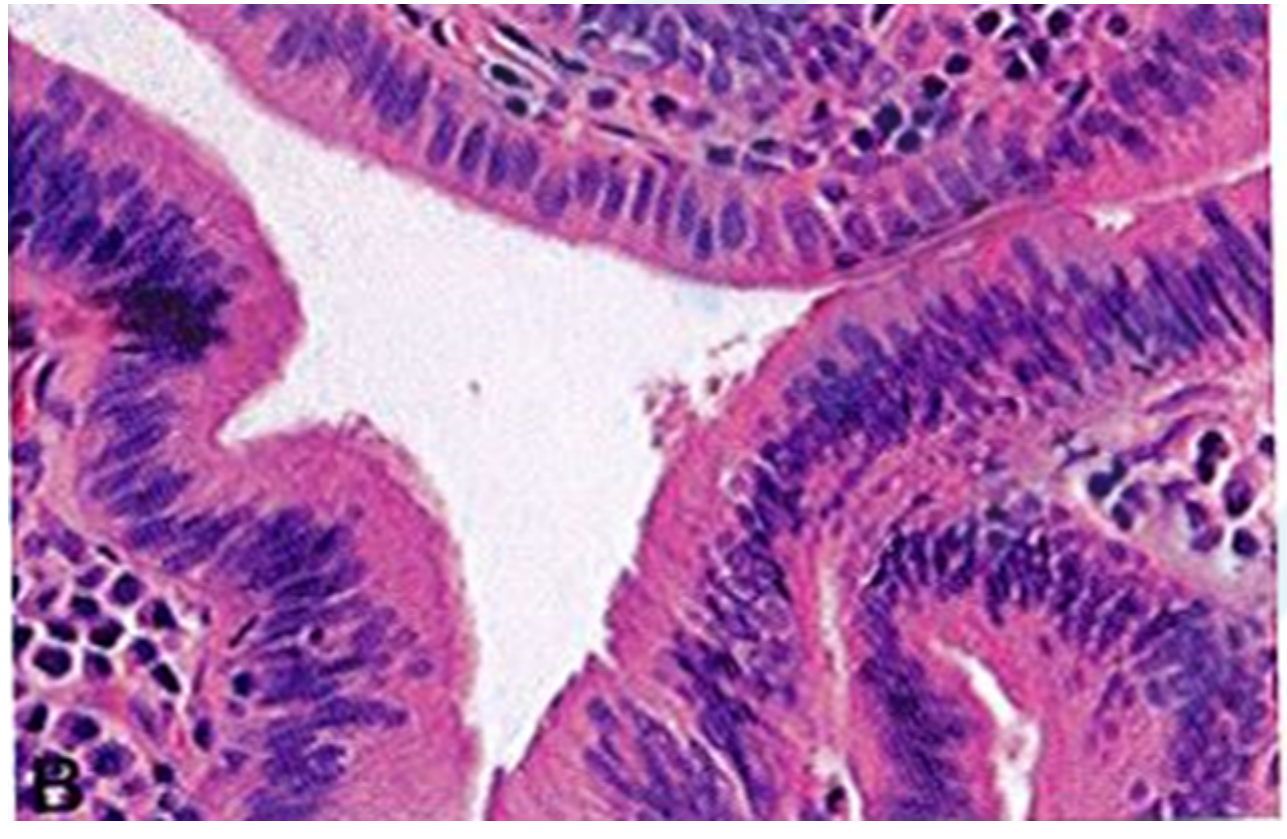
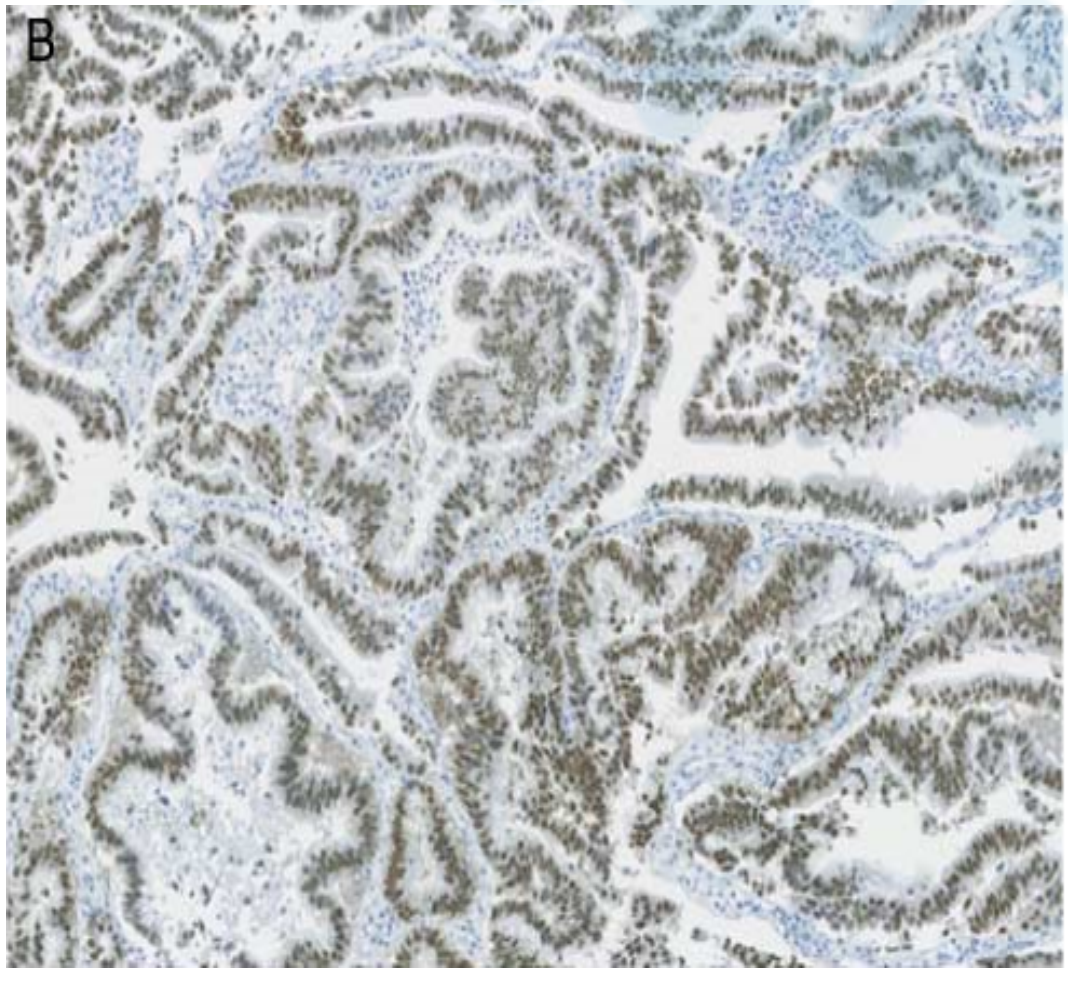
- **The present study aimed to identify the pathologic and genetic characteristics of intestinal subtype of intraductal papillary neoplasm of the bile duct (iIPNB)**
- **Showing columnar cells with pseudostratified, cigar-shaped nuclei, and basophilic or amphophilic cytoplasm with the diffuse immunohistochemical expression of CK20 and/or CDX2.**

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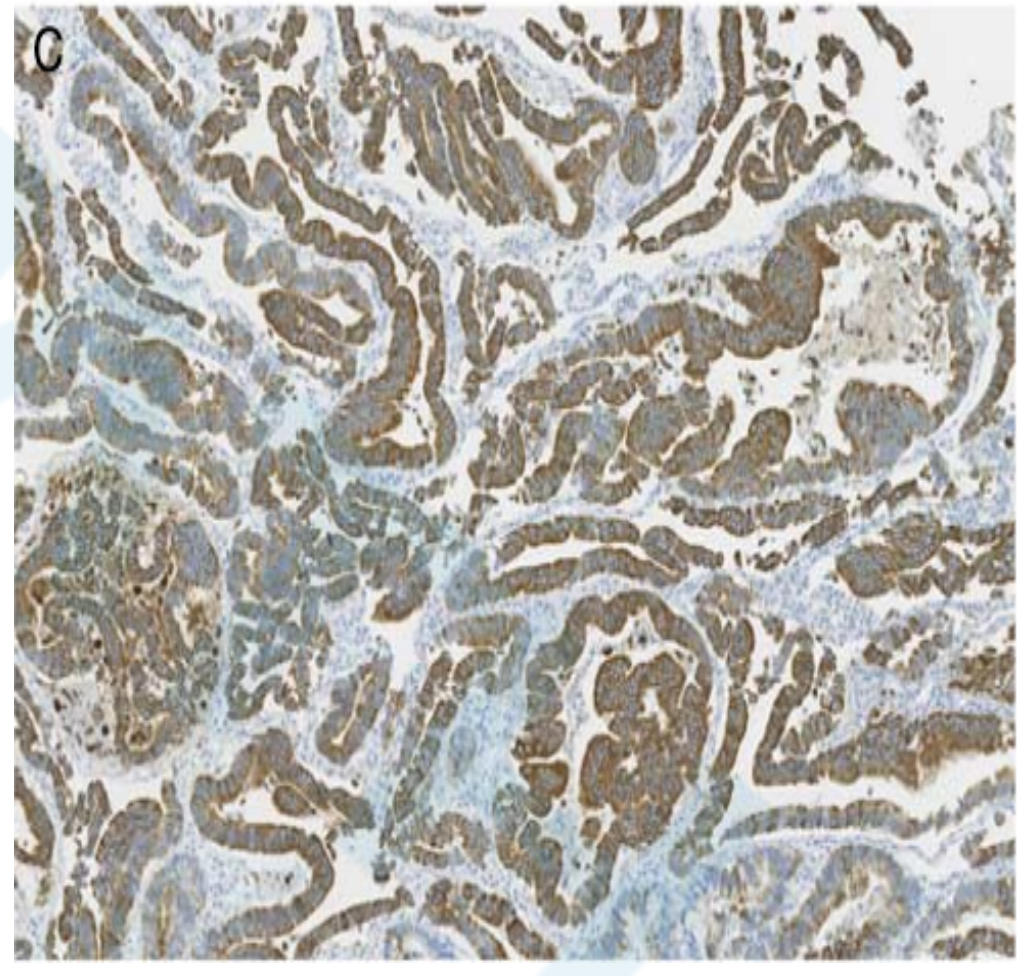
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MATERIALS AND METHODS

- **IPNB and IPMN were pathologically defined according to the 2010 WHO Classification of Tumors of the Digestive System.**
- **We collected a total of 69 cases of IPNB**
  Shizuoka Cancer Center
  Shizuoka (2002-2014) (n=63),
  Fukui Saiseikai Hospital, Fukui (2004-2017) (n=3)
  Shizuoka Medical Center, Shizuoka (n=3).

- IPNBs were classified into intrahepatic and extrahepatic IPNBs, according to their anatomic locastion.
- Intraductal neoplasms of the common channel and duodenal parts of the ampulla of Vater were excluded.
- Papillary tumors of the gallbladder and cystic ducts were not included.

- **A total of 111 cases of IPMN**

Fukui Saiseikai Hospital, Fukui (2004-2017)
Juntendo University School of Medicine (2000-2014), Tokyo.

- **22 intestinal subtype (mean age, 68y, range, 53 to 78y; male, n=13; female, n=9);**

RESULTS

The Main Clinicopathologic Features of iIPNBs

TABLE 1. Clinicopathologic Features of the Intestinal Subtype of IPNB

	Total Cases	Intrahepatic Cases	Extrahepatic Cases
Case Number	**34 Cases**	**6 Cases**	**28 Cases**
Age (mean ± SD, range) (y)	69.3 ± 9.6, 37-82	68.1 ± 9.5, 64-82	73 ± 6.5, 37-82
Sex (M:F)	23:11	4:2	19:9
Structures		Villous-papillary pattern (mainly villous in 5 cases and mainly papillary in one case)	Mainly papillary pattern with tubular and/or villous components (all cases)
Grades (dysplasia)			
Predominantly high	26 cases	2 cases	24 cases*
High with low/int areas	8 cases	4 cases	4 cases
Complicasted lesions			
None	18 cases	6 cases	12 cases*
Present	16 cases	0 case	16 cases
Stromal invasion			
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Excessive mucin secretion			
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*$P < 0.05$.
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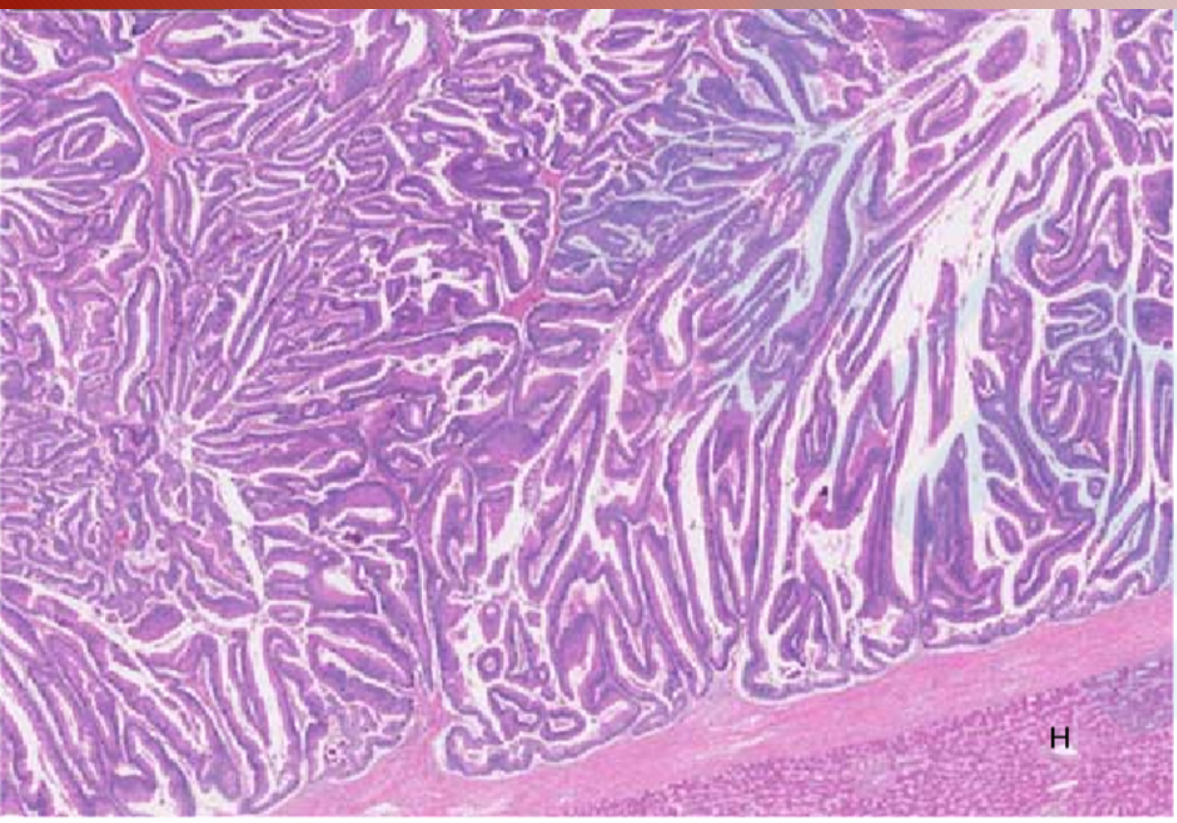
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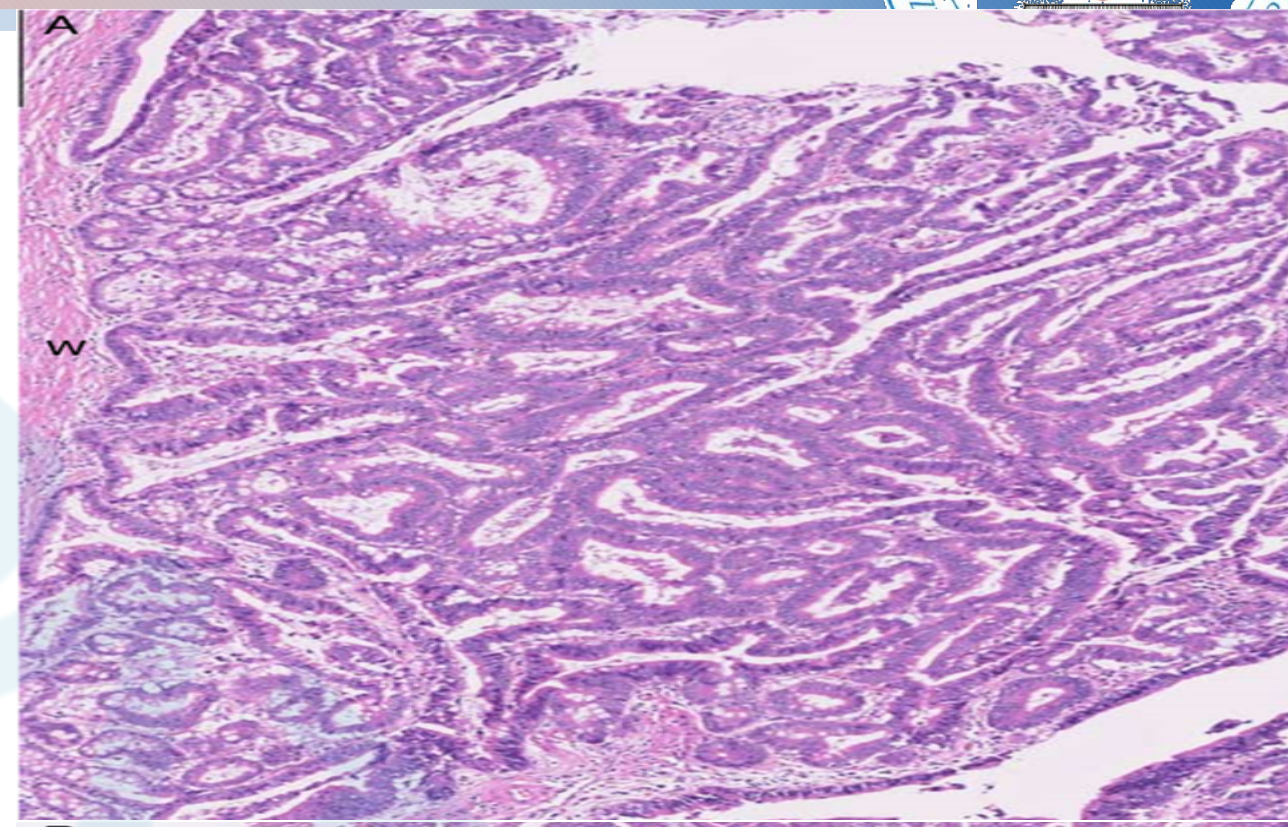
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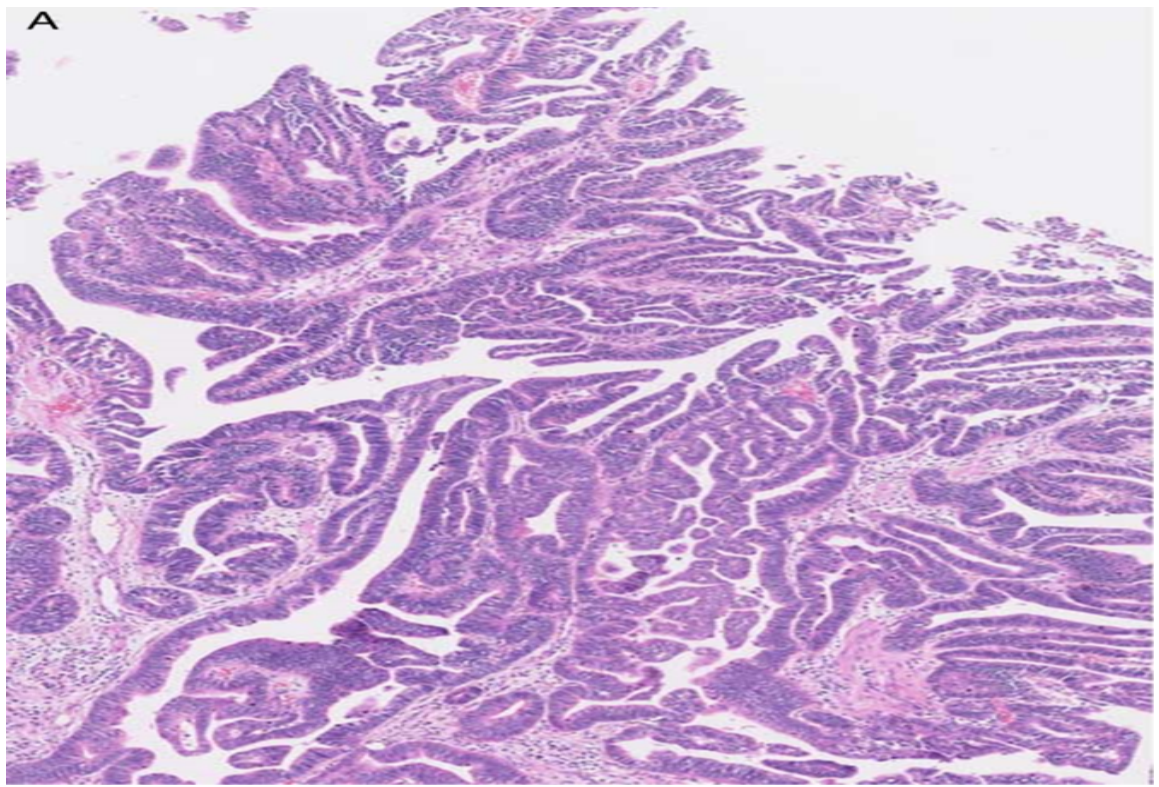
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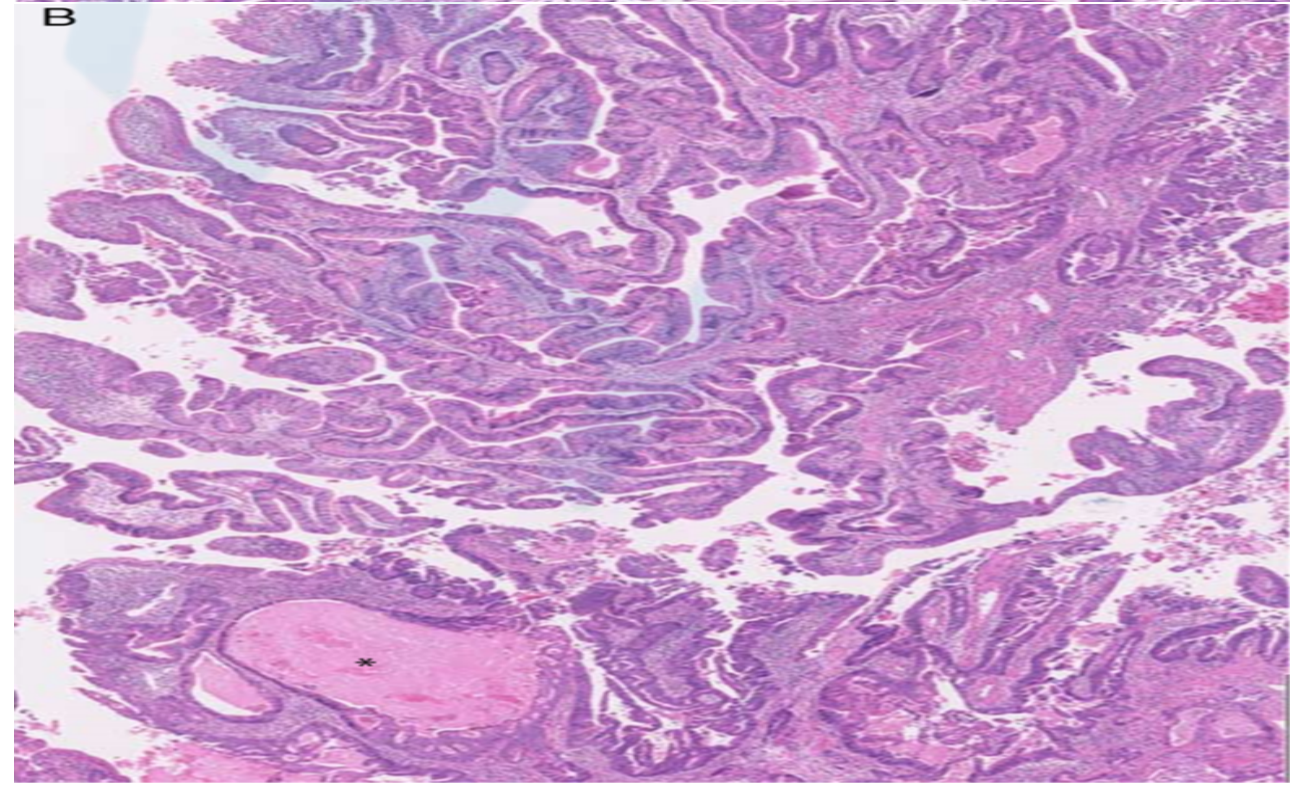
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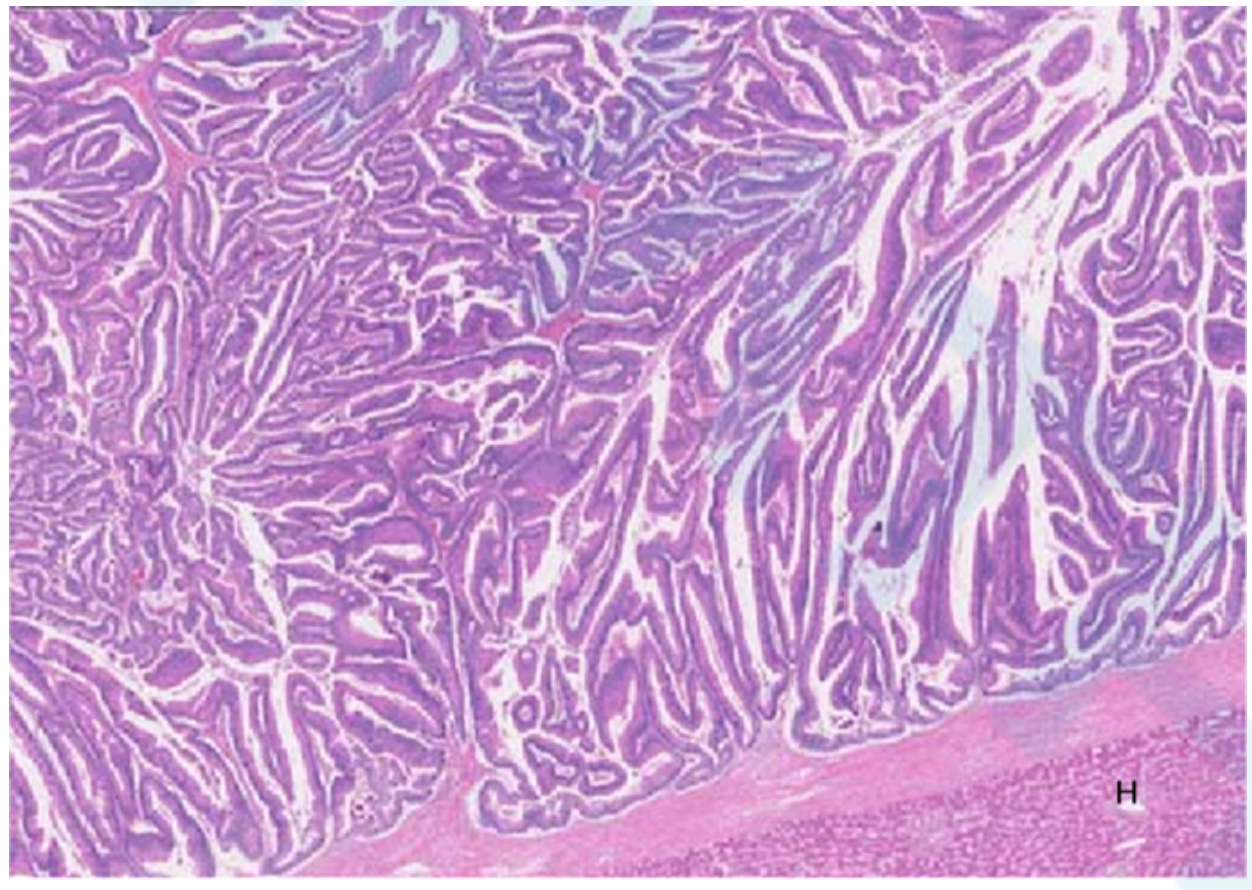
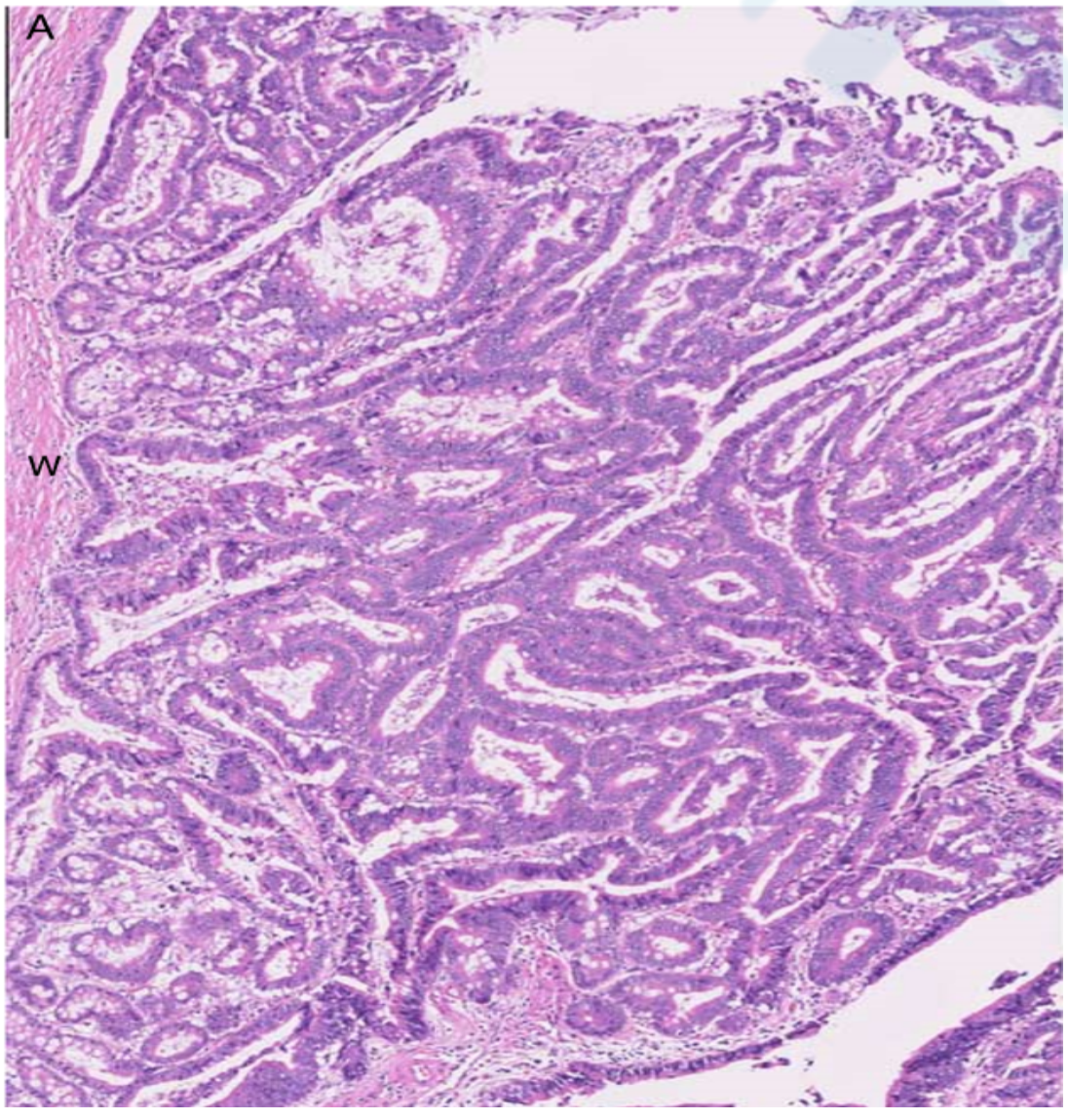
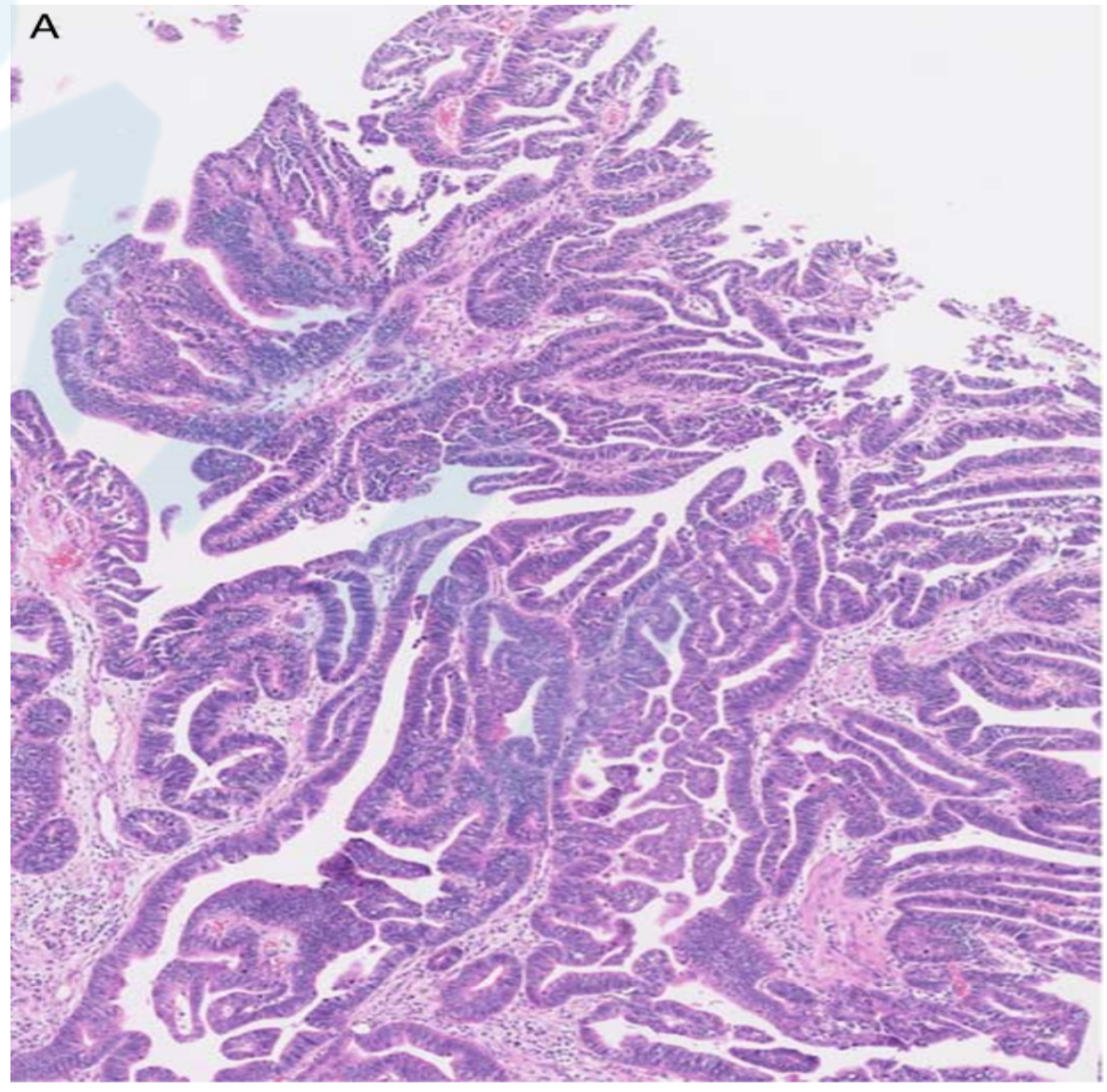
- **intrahepatic IPNBs showed rather regular villous and papillary patterns in variable proportions.**

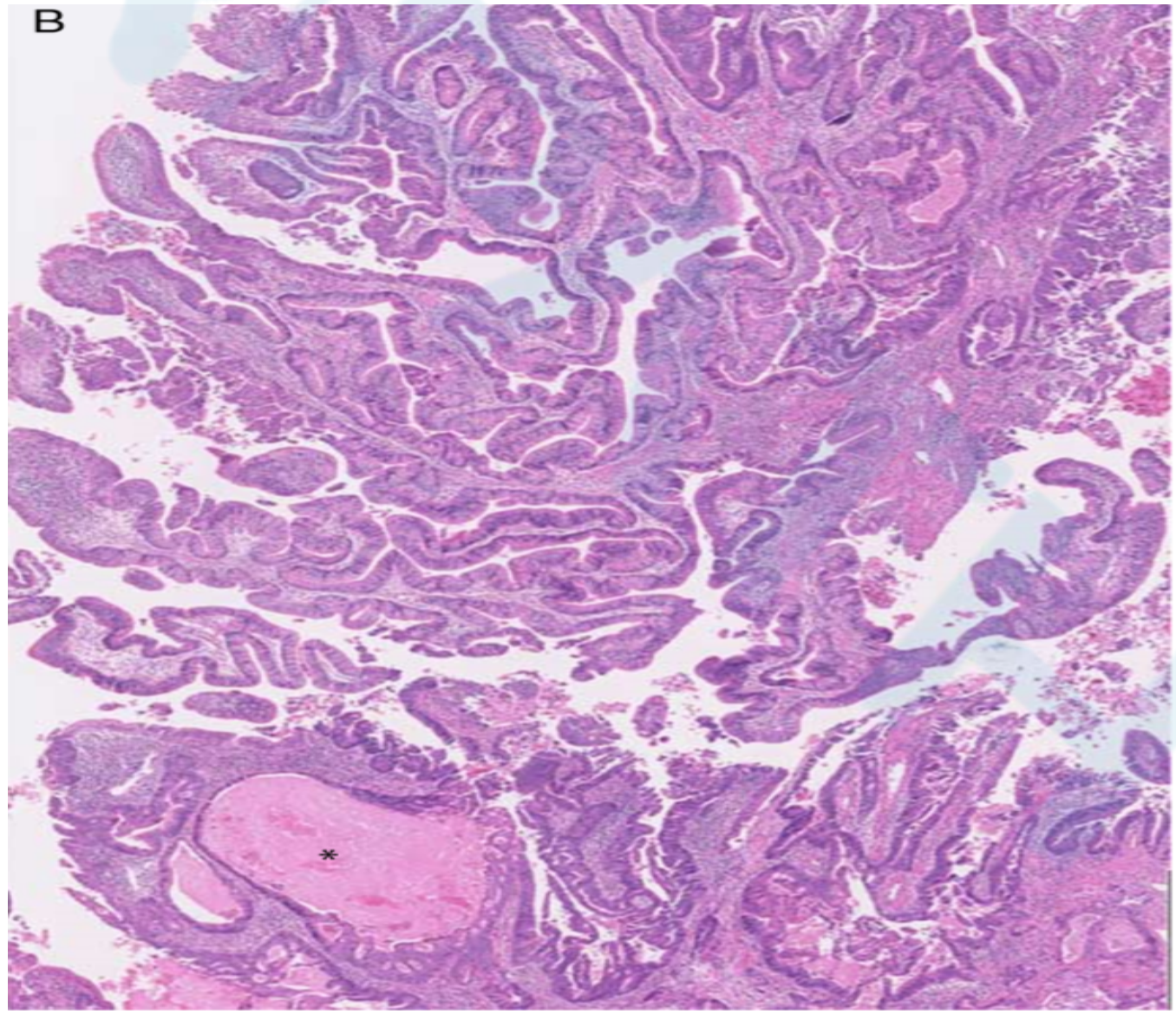


- **In contrast, in extrahepatic IPNBs, papillary patterns that included irregular or deformed papillae.**





- **More complicated lesions such as foci of compact or solid, crowded tubular or cribriform areas, and microcystic changes were admixed with the papillary lesions .**



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- Based on the degree of cellular and nuclear atypia in accordance with the WHO 2010.
- The intraductal portions of IPNB were classified as intraepithelial neoplasia of low, intermediate,and high-grade dysplasia (in situ carcinoma).
- In this study, low and intermediate grades were grouped together as “low/int grade.”

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- Invasion was found at the base and/or fibrovascular stalk near the base: 2 of 6 cases of intrahepatic iIPNB and 16 of 28 cases of extrahepatic iIPNB
- In these iIPNB cases, stromal invasion was found in high-grade areas.

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- **Excessive mucin hypersecretion in the affected duct lumen was frequenty found in intrahepatic iIPNBs (all cases).**

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- **Intracellular mucin droplets were frequently observed in extrahepatic IPNBs and in almost all cases of intrahepatic IPNBs.**

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Immunohistochemical Analyses of Intrahepatic and Extrahepatic iIPNBs and iIPMNs

	Intrahepatic iIPNB (n = 6)	Extrahepatic iIPNB (n = 28)	Pancreatic iIPMN (n = 22)
MUC1			
−	5	17	
+/++	1/0	5/6	4/1
MUC2			
−	3	23	4**
+/++	0/3	5/0	6/12
MUC5AC			
−	1	11*	0**
+/++	2/3	3/4	5/17
MUC6			
−	6	24	22
+/++	0/0	3/1	0/0
CDX2			
−	0	1	0
+/++	2/4	2/25	6/16
CD10			
−	6	10**	20**
+/++	0/0	7/11	2/0
CK7			
−	2	2	3
+/++	0/4	8/18	1/18
CK20			
−	3	9	4
+/++	0/3	6/13	7/11
S100P			
−	0	1	0
+/++	3/3	16/11	8/14

Gene Mutations

- **Mutations of somatic genes (TP53, APC, SMAD4, PIK3CA, GNAS, KRAS, CTNNB1, STK11, FBXW7, BRAF, NRAS, PDGFRA, FGFR2, and FOXL2) were detected in 18 of the 21 iIPNB cases.**

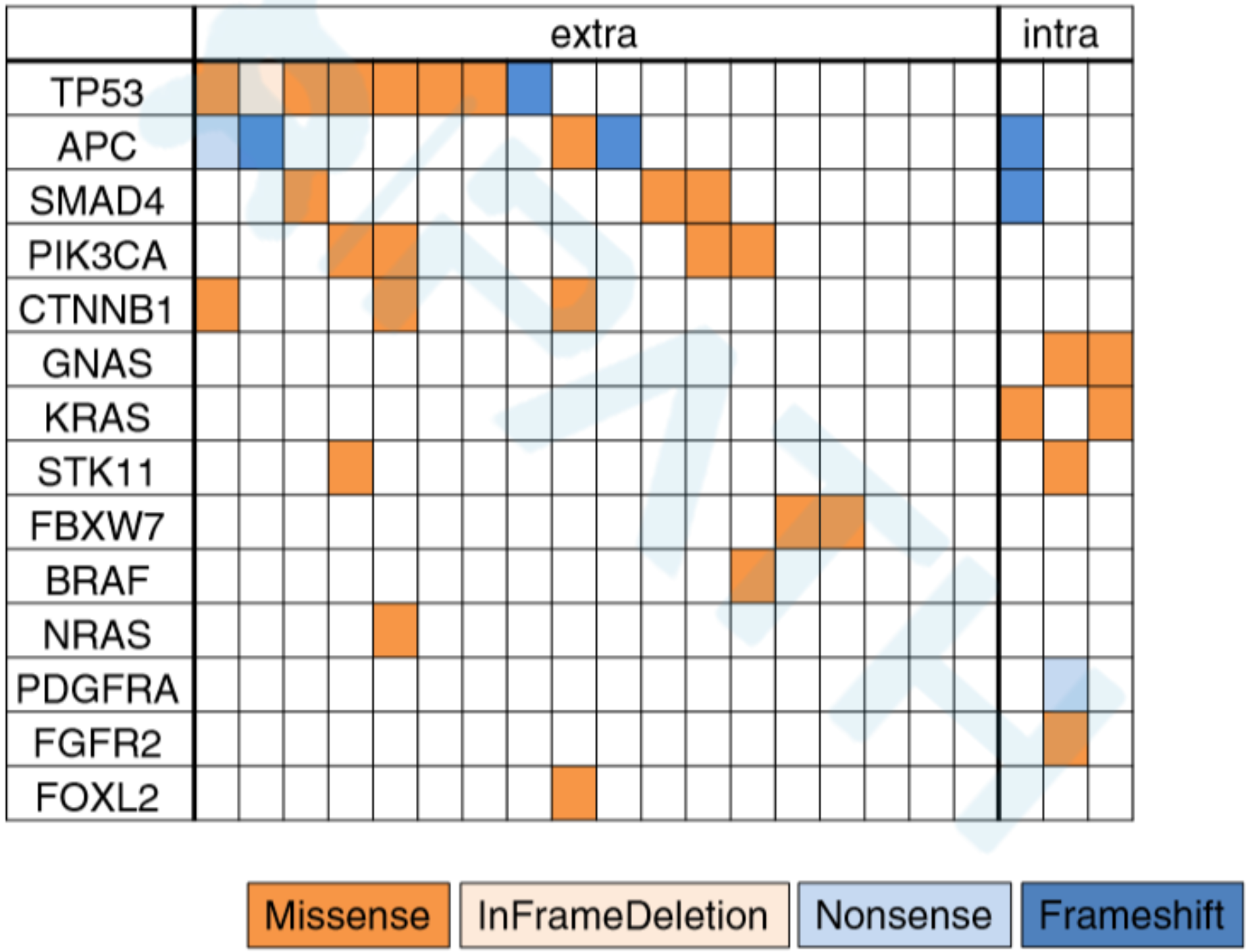
extra
intra
TP53
APC
SMAD4
PIK3CA
CTNNB1
GNAS
KRAS
STK11
FBXW7
BRAF
NRAS
PDGFRA
FGFR2
FOXL2
Missense
InFrameDeletion
Nonsense
Frameshift

TABLE 5. Frequency of Muctations of 14 Genes in iIPNBs (Extrahepatic and Intrahepatic) Examined in this Study and in iIPMNs Reported in the Literatures

	iIPNB (%)		
	Extra (n = 18)	Intra (n = 3)	iIPMN[21–27,30,32] (Intestinal Subtype) (%)
TP53	44	0	6-8 (intraductal)
APC	22	33.3	0
SMAD4	17	33.3	0
PIK3CA	22	0	0
CTNNB1	17	0	6
GNAS	0	66.7	74 (intraductal)-83
KRAS	0	66.7	63 (intraductal)-86
SKT11	9	33.3	6
FBXW7	11	0	No report
BRAF	5.6	0	8
NRAS	5.6	0	0
PDGFRA	0	33.3	33
FGFR2	0	33.3	No report
FOXL2	6	0	No report

DISCUSSION

- In conclusion, iIPNBs accounted for almost half of IPNBs and showed different histologic characteristics and biological aggressiveness, as well as genetic alterations according to their anatomic location along the biliary tree.
- Intrahepatic IPNBs presented as villous papillary neoplasms, while extrahepatic IPNBs were papillary-predominant neoplasms admixed with villous or tubular components.
- Extrahepatic IPNBs showed predominantly high-grade dysplasia, more complicated histology, and aggressive features in comparison to intrahepatic IPNBs.
- Intrahepatic iIPNBs frequently expressed MUC5AC and showed GNAS and KRAS mutations—as seen in iIPMNs—while extrahepatic iIPNBs frequently expressed CD10 and frequent showed TP53 and PICK3CA mutations.

WHO classification of tumours of the liver and intrahepatic bile ducts

Benign hepatocellular tumours
8170/0 Hepatocellular adenoma
HNF1A-inactivated hepatocellular adenoma
Inflammatory hepatocellular adenoma
B-catenin-activated hepatocellular adenoma
B-catenin-activated inflammatory hepatocellular adenoma

Malignant hepatocellular tumours and precursors
8170/3 Hepatocellular carcinoma NOS
8171/3 Hepatocellular carcinoma, fibrolamellar
8172/3 Hepatocellular carcinoma, scirrhous
8174/3 Hepatocellular carcinoma, clear cell type
Hepatocellular carcinoma, steatohepatitic
Hepatocellular carcinoma, macrotrabecular massive
Hepatocellular carcinoma, chromophobe
Hepatocellular carcinoma, neutrophil-rich
Hepatocellular carcinoma, lymphocyte-rich
8970/3 Hepatoblastoma NOS

Benign biliary tumours and precursors
8160/0 Bile duct adenoma
9013/0 Adenofibroma NOS
8148/0 Biliary intraepithelial neoplasia, low grade
8148/2 Biliary intraepithelial neoplasia, high grade
8503/0 Intraductal papillary neoplasm with low-grade intraepithelial neoplasia
8503/2 Intraductal papillary neoplasm with high-grade intraepithelial neoplasia
8503/3 Intraductal papillary neoplasm with associated invasive carcinoma
8470/0 Mucinous cystic neoplasm with low-grade intraepithelial neoplasia
8470/2 Mucinous cystic neoplasm with high-grade intraepithelial neoplasia
8470/3 Mucinous cystic neoplasm with associated invasive carcinoma

Malignant biliary tumours
8160/3 Cholangiocarcinoma
Large duct intrahepatic cholangiocarcinoma
Small duct intrahepatic cholangiocarcinoma
8020/3 Carcinoma, undifferentiated, NOS
8180/3 Combined hepatocellular carcinoma and cholangiocarcinoma
8240/3 Neuroendocrine tumour NOS
8240/3 Neuroendocrine tumour, grade 1
8249/3 Neuroendocrine tumour, grade 2
8249/3 Neuroendocrine tumour, grade 3
8246/3 Neuroendocrine carcinoma NOS
8013/3 Large cell neuroendocrine carcinoma
8041/3 Small cell neuroendocrine carcinoma
8154/3 Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)

WHO classification of tumours of the gallbladder and extrahepatic bile ducts

Benign epithelial tumours and precursors

8140/0	Adenoma NOS
8148/0	Biliary intraepithelial neoplasia, low grade
8148/2	Biliary intraepithelial neoplasia, high grade
8503/0	Intracystic papillary neoplasm with low-grade intraepithelial neoplasia
8503/2	Intracystic papillary neoplasm with high-grade intraepithelial neoplasia
8503/3	Intracystic papillary neoplasm with associated invasive carcinoma
8503/0	Intraductal papillary neoplasm with low-grade intraepithelial neoplasia
8503/2	Intraductal papillary neoplasm with high-grade intraepithelial neoplasia
8503/3	Intraductal papillary neoplasm with associated invasive carcinoma

Malignant epithelial tumours

8140/3	Adenocarcinoma NOS
8144/3	Adenocarcinoma, intestinal type
8310/3	Clear cell adenocarcinoma NOS
8470/3	Mucinous cystic neoplasm with associated invasive carcinoma
8480/3	Mucinous adenocarcinoma
8490/3	Poorly cohesive carcinoma
8503/3	Intracystic papillary neoplasm with associated invasive carcinoma
8070/3	Squamous cell carcinoma NOS
8020/3	Carcinoma, undifferentiated, NOS
8560/3	Adenosquamous carcinoma
8160/3	Cholangiocarcinoma
8240/3	Neuroendocrine tumour NOS
8240/3	Neuroendocrine tumour, grade 1
8249/3	Neuroendocrine tumour, grade 2
8249/3	Neuroendocrine tumour, grade 3
8246/3	Neuroendocrine carcinoma NOS
8013/3	Large cell neuroendocrine carcinoma
8041/3	Small cell neuroendocrine carcinoma
8154/3	Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)

These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2) {1378A}. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.

Table 9.03 Characteristics of intraductal papillary neoplasms of the bile ducts based on similarities to their pancreatic counterparts, according to the Japan–Korea Cooperative Study Group {2295}

Characteristic	Type 1	Type 2
Preferential location	Intrahepatic bile ducts	Extrahepatic bile ducts
Gross features of ducts	Cystic, cylindrical dilatation	Cylindrical, fusiform dilatation
Excessive mucin	Frequent	Rare
Histology		
Lining epithelia	Regular, homogeneous Papillary > tubular	Irregular, complex Papillary > tubular; foci of cribriform and solid pattern
Fibrous core	Fine fibrovascular stroma	Fine vascular, focally fibrotic stroma
Subtype	Gastric, intestinal	Intestinal, pancreatobiliary
Grade	Mostly high grade, with foci of low/intermediate grade; infrequently low/intermediate grade	Always high grade, sometimes with foci of low/intermediate grade
Stromal invasion	Less common (< 50%) and minimal, occasionally nodular	Common (> 80%) and minimal, mild
Similarity to IPMN	Similar	Variably different
Aggressiveness	Less aggressive	More aggressive than type 1
Postoperative course	More favourable	Worse than type 1

IPMN, intraductal papillary mucinous neoplasm.

- **1.**肝内胆管空间较小，肝外胆管空间较大？
- **2.**肝外胆管毗邻胰管，但差异巨大？
- **2.**肠型**IPNB**和其他亚型在免疫表型和基因方面差异？
- **3.**其他亚型**IPNB**和**IPMN**各亚型之间的异同？

谢谢！