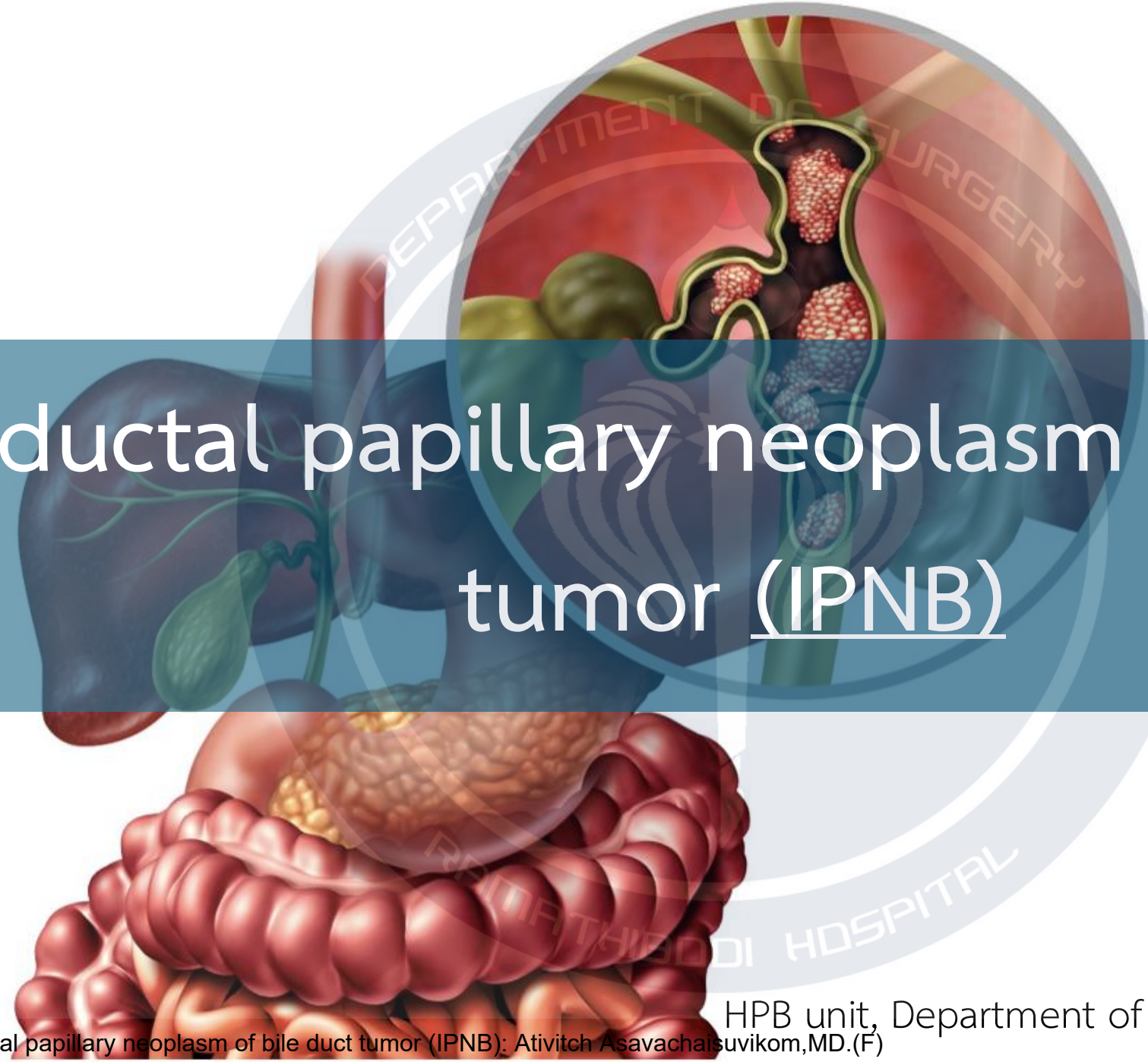


Intraductal papillary neoplasm of bile duct tumor (IPNB)

F Ativitch Asavachaisuvikom

Advisor : Dr. Wikarn Suragul

HPB unit, Department of Surgery, Ramathibodi Hospital

OUTLINE

- Introduction
- Etiology and diagnosis
- Histology and morphology subtype
- Management
- Post operative outcome

Introduction

Concepts

- Intraductal papillary neoplasm of the bile duct (IPNB) is a rare variant of bile duct tumors characterized by papillary growth[1]
- Spectrum of "**premalignant lesion towards invasive cholangiocarcinoma**"
- Include biliary papilloma, biliary adenoma, papillomatosis, cystadenomas and biliary cystadenomas.

Ohtsuka M, Shimizu H, Kato A, Yoshitomi H, Furukawa K, Tsuyuguchi T, et al. Intraductal papillary neoplasms of the bile duct. Int J Hepatol 2014;2014(5): e459091.

Premalignant lesion

- Biliary epithelial neoplasm(BilIN)
- Intraductal papillary neoplasm of the bile duct(IPNB)
- Intraductal tubular neoplasm of the bile duct(ITNB)
- Mucinous cystic neoplasms(MCN)

Nakanuma Y, Kakuda Y. Pathologic classification of cholangiocarcinoma: New concepts. Best Pract Res Clin Gastroenterol. 2015 Apr;29(2):277-93. doi: 10.1016/j.bpg.2015.02.006. Epub 2015 Feb 17. PMID: 25966428.

Premalignant lesion	Gross morphology type of CCA
BilIN	Periductal-Infiltrating type of iCCA Flat or nodular sclerosing type of pCCA/dCCA
IPNB/ITNB	Intraductal growth type of iCCA Papillary type of pCCA/dCCA
MCN	MCN associated with invasive carcinoma
Unidentified lesion	Mass-forming type of iCCA

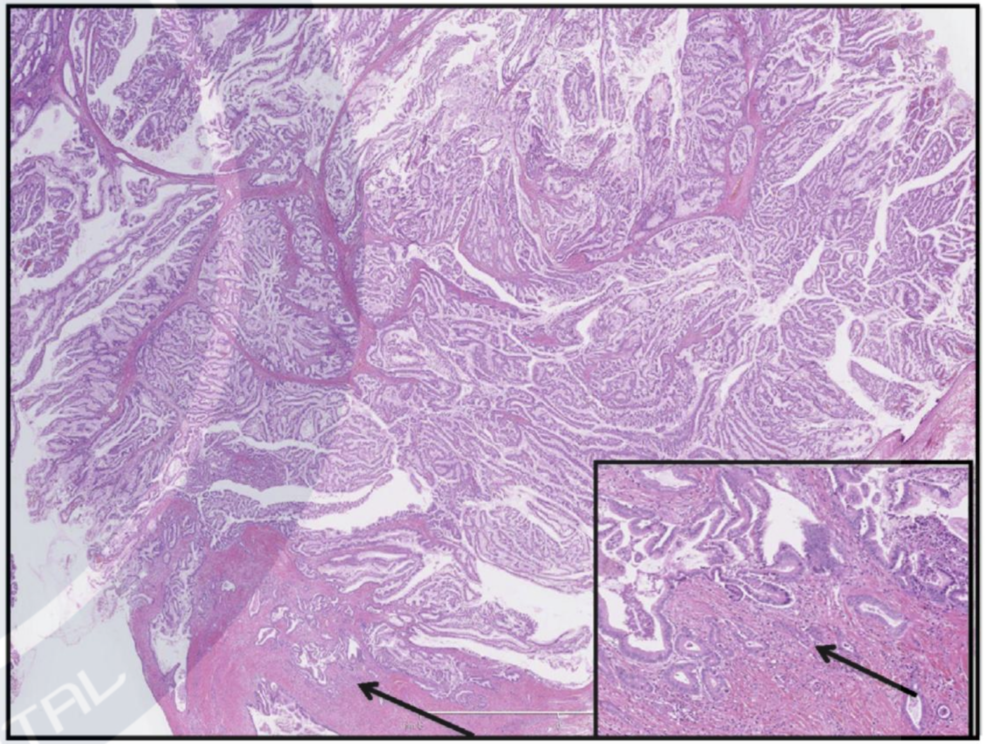
Nakanuma Y, Kakuda Y. Pathologic classification of cholangiocarcinoma: New concepts. Best Pract Res Clin Gastroenterol. 2015 Apr;29(2):277-93. doi: 10.1016/j.bpg.2015.02.006. Epub 2015 Feb 17. PMID: 25966428.

Biliary tract	Pancreas
a. Conventional cholangiocarcinoma of the perihilar and distal bile duct	Pancreatic duct adenocarcinoma
b. Biliary intraepithelial neoplasm (BilIN)	Pancreatic intraepithelial neoplasm (PanIN)
c. Intraductal papillary neoplasm of the bile duct (IPNB)	Intraductal papillary mucinous neoplasm (IPMN)
i. Involvement of bile duct	i. Main pancreatic duct type
ii. Involvement of peribiliary glands	ii. Branch pancreatic duct type
d. Intraductal tubular neoplasm of the bile duct (ITNB)	Intraductal tubulopapillary neoplasm (ITPN)
e. Mucinous cystic neoplasm	Mucinous cystic neoplasm

Nakanuma Y, Kakuda Y. Pathologic classification of cholangiocarcinoma: New concepts. Best Pract Res Clin Gastroenterol. 2015 Apr;29(2):277-93. doi: 10.1016/j.bpg.2015.02.006. Epub 2015 Feb 17. PMID: 25966428.

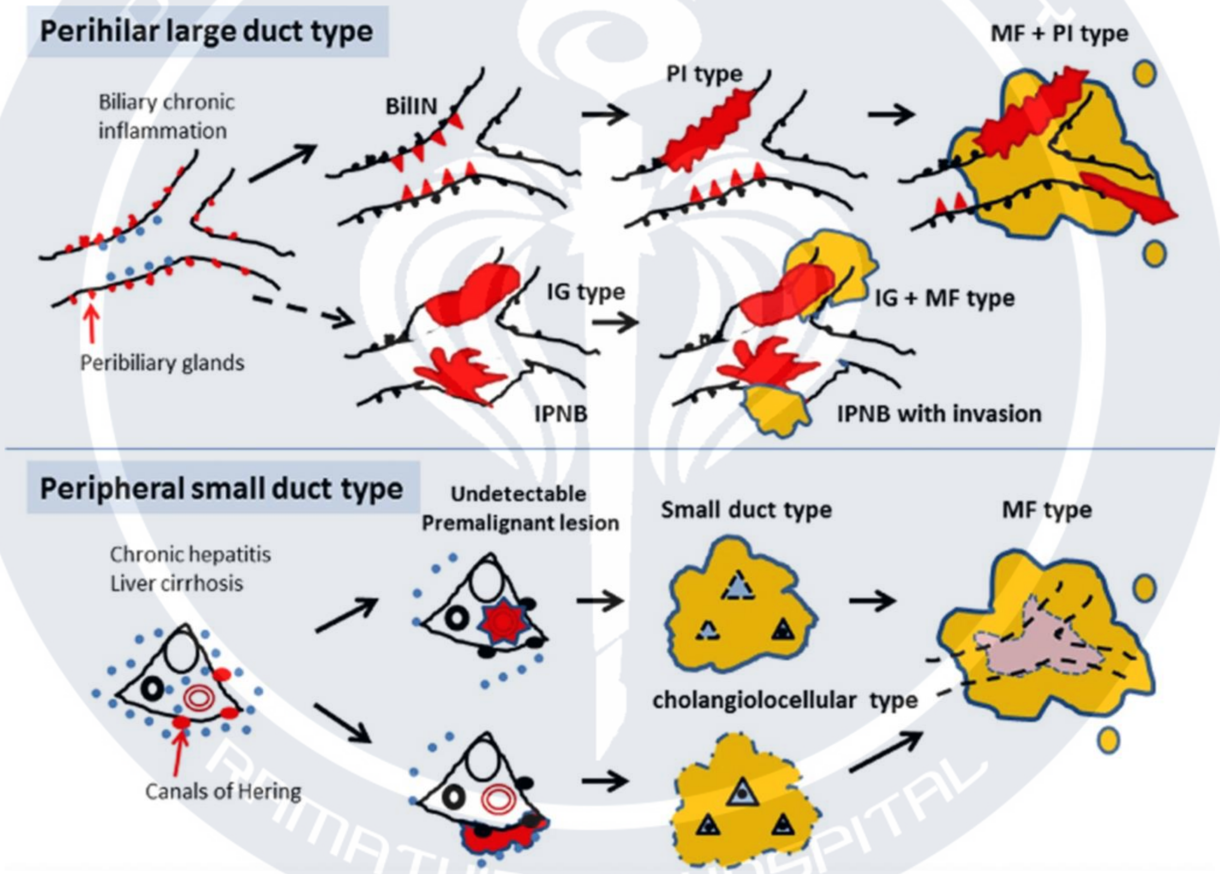
IPNB

- Dilated intrahepatic and extrahepatic bile ducts filled with papillary or villous biliary neoplasm that covers delicate fibrovascular stalks
- The height of such lesions usually exceeds 5 mm.
- Slow progression tumor : Adenoma-carcinoma sequence
- Four phenotype
  - Intestinal type
  - Pancreatobiliary type
  - Oncocytic type
  - Gastric type



Nakanuma Y, Kakuda Y. Pathologic classification of cholangiocarcinoma: New concepts. Best Pract Res Clin Gastroenterol. 2015 Apr;29(2):277-93. doi: 10.1016/j.bpg.2015.02.006. Epub 2015 Feb 17. PMID: 25966428.

Pathogenesis



Aishima S, Oda Y (2015). Pathogenesis and classification of intrahepatic cholangiocarcinoma: different characters of perihilar large duct type versus peripheral small duct type. J Hepatobiliary Pancreat Sci, 2, 94-100

Etiology and diagnosis

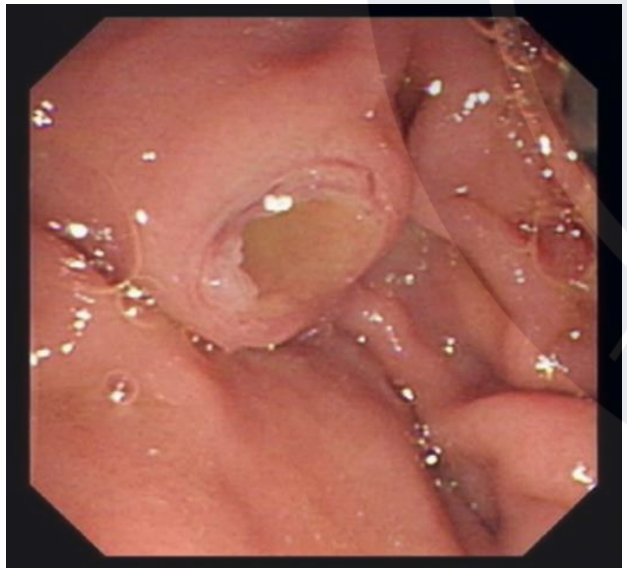
Review article

Intraductal papillary neoplasm of the bile duct – A comprehensive review

Marek Krawczyk [a,*], Bogna Ziarkiewicz-Wróblewska [b], Joanna Podgórska [c], Jakub Grzybowski [b], Beata Gierej [b], Piotr Krawczyk [a], Michał Grąt [a], Oskar Kornasiewicz [a], Michał Skalski [a], Tadeusz Wróblewski [a]

[a] *Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland*
[b] *Department of Pathomorphology, Medical University of Warsaw, Warsaw, Poland*
[c] *2nd Department of Clinical Radiology, Medical University of Warsaw, Warsaw, Poland*

Very thick mucous, Fish mouth appearance



		No of Patients n (%)	Own Material n (%)
Presentation	Abdominal pain	164 (42%)	9 (36%)
	Mechanical jaundice	130 (33%)	12 (48%)
	Cholangitis	56 (14%)	6 (24%)
	Asymptomatic	48 (12%)	3 (12%)
Diagnostic imaging	CT	220 (63%)	19 (76%)
	MR	142 (40%)	14 (56%)
	USS	34 (10%)	13 (52%)
	ERCP	218 (62%)	12 (48%)
Imaging findings	Intraductal mass	147 (31%)	8 (32%)
	Duct dilatation	126 (27%)	9 (30%)
Serum tumor markers	CA 19-9	164 (42%)	6 (24%)
	CEA	440 (25%)	

Systematic Review and Meta-analysis of Current Experience in Treating IPNB

Clinical and Pathological Correlates

Alex N. Gordon-Weeks, MBChB, BSc, MRCS, DPhil, Keaton Jones, MRCS,† Elinor Harriss, MSc, MA,‡ Adrian Smith, MBBS, DPhil,§ and Michael Silva, MBBS, MD, MS, FRCS (Gen), FRCS Ed¶*

ANNALS OF SURGERY

TABLE 1. Clinical Presentation, Etiology, and Investigation of IPNB

		No. of Patients (%)	Total Patients	References
Presentation	Pain	164 (42)	391	7,9,12–14,28,31–34
	Jaundice	130 (33)		
	Cholangitis	56 (14)		
	Asymptomatic	48 (12)		
Possible etiological association	Hepatolithiasis; *C. sinensis*	68 (27); 69 (27)	253	12,14,22,33
Diagnostic imaging	CT	220 (63)	349	3,12,14,31–37
	ERCP	218 (62)		
	MRI	142 (40)		
	USS	34 (10)		
	EUS	10 (9)	104	14,29
Imaging findings	Intraductal mass	147 (31)	387	12,13,31,33,35,37–39
	Duct dilatation	126 (27)		
	Duct ectasia	29 (6)		
	Duct stricture	13 (3)		

Gordon-Weeks, Alex N. MBChB, BSc, MRCS, DPhil; Jones, Keaton MRCS; Harriss, Elinor MSc, MA; Smith, Adrian MBBS, DPhil; Silva, Michael MBBS, MD, MS, FRCS (Gen), FRCS Ed. Systematic Review and Meta-analysis of Current Experience in Treating IPNB: Clinical and Pathological Correlates. Annals of Surgery 263(4):p 656-663, April 2016.

International Journal of General Medicine

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ORIGINAL RESEARCH

Serum IgG as a Marker for *Opisthorchis viverrini*-Associated Cholangiocarcinoma Correlated with HER2 Overexpression

This article was published in the following Dove Press journal:
International Journal of General Medicine

Conclusion: We found a high prevalence of serum IgG for OV-positive CCA patients and a correlation with overexpression of HER2. Moreover, IgG for OV and HER2 expression indicated poor survival of CCA. Therefore, future clinical studies for anti-HER2 treatments should focus on OV-associated CCA.

Narong Khuntikeo [1,2]

[1]Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; [2]Cholangiocarcinoma Research Institute (CARI), Khon Kaen University, Khon Kaen, Thailand; [3]Faculty of Associated Medical Sciences, Khon Kaen University, Khon Kaen, Thailand; [4]Department of Pathology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; [5]Department of Parasitology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; [6]Department of Biochemistry, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; [7]Department of Epidemiology and Biostatistics, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand

regression was used to determine factors that affected CCA patient survival.

Results: IgG for OV were positive in 162 cases, and the prevalence was 73.3% (95% CI=68.0–78.7). About three quarters (78.3%) had large duct type tumors and concomitant intraductal papillary neoplasm of bile ducts (IPNB) occurred in 92 (50%) cases. HER2 expression was positive in 94 (61.4%) cases. Positive PD-L1 and FGFR2 expression occurred in 125 (83.9%) and 100 (67.1%) cases. IgG for OV had no significant correlation to any histological feature but had significant correlation with HER2 overexpression with adjusted OR=2.32 (95% CI=1.09–4.96, *P*=0.03). Cases of CCA with OV IgG positive had a significantly poor prognosis with adjusted HR=1.66 (95% CI=1.13–2.43, *P*=0.01).

Conclusion: We found a high prevalence of serum IgG for OV-positive CCA patients and a correlation with overexpression of HER2. Moreover, IgG for OV and HER2 expression indicated poor survival of CCA. Therefore, future clinical studies for anti-HER2 treatments should focus on OV-associated CCA.

Keywords: survival, intraductal type, FGFR2, PD-L1, immunoglobulin G, fluke-associated CCA

ANNALS of Hepatology
The Official Journal of the Mexican Association of Hepatology, the Latin-American Association for Study of the Liver and the Canadian Association for the Study of the Liver

ORIGINAL ARTICLE

September-October, Vol. 17 No. 5, 2018: 802-809

Association between Repeated Praziquantel treatment and Papillary, and Intrahepatic Cholangiocarcinoma

Vor Luvira,* Supot Kamsa-ard,† Siriporn Kamsa-ard,‡ Varisara Luvira,§
Tharatip Srisuk,* Ake Pugkhem,* Chawalit Pairojkul,‖ Vajarabhongsa Bhudhisawasdi*

* Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.
† Cancer Unit, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.
‡ Department of Epidemiology and Biostatistics, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand.
§ Department of Community Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.
‖ Department of Pathology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.

Table 2. Crude and adjusted ORs for Intrahepatic CCA and number of PZQ treatments.

Characteristic	Intrahepatic CCA (n = 108), (%)	Control (n = 423), (%)	Crude OR	Adjusted OR	95% CI	p-value
1. Number of PZQ treatments (times)						0.011
0	47.2	66.0	1	1	-	
1	33.3	26.4	1.82	1.54	0.92-2.55	
2	9.3	4.9	3.15	2.28	0.91- 5.73	
More than 2	10.2	2.8	5.63	4.21	1.61-11.05	
	100.0	100.0				

Table 5. Crude and adjusted ORs for Papillary carcinoma and number of PZQ treatments.

Characteristics	Papillary CCA (n = 82), (%)	Control (n = 328),(%)	Crude OR	Adjusted OR	95% CI	p-value
1. Number of PZQ treatments (times)						0.066
0	46.3	64.9	1	1	-	
1	31.7	26.8	1.78	1.45	0.80-2.63	
2	11.0	4.9	4.04	2.96	1.06-8.24	
More than 2	11.0	3.4	5.25	3.24	1.09-9.66	
	100.0	100.0				

After adjustment for smoking behavior, alcohol consumption, history of cancer in family, and consuming raw freshwater fish.

Conclusion : The current study found an association between papillary and intrahepatic CCA and repeated use of PZQ treatment. We suggest further study on the risk factors for papillary and tubular CCA should be performed separately.

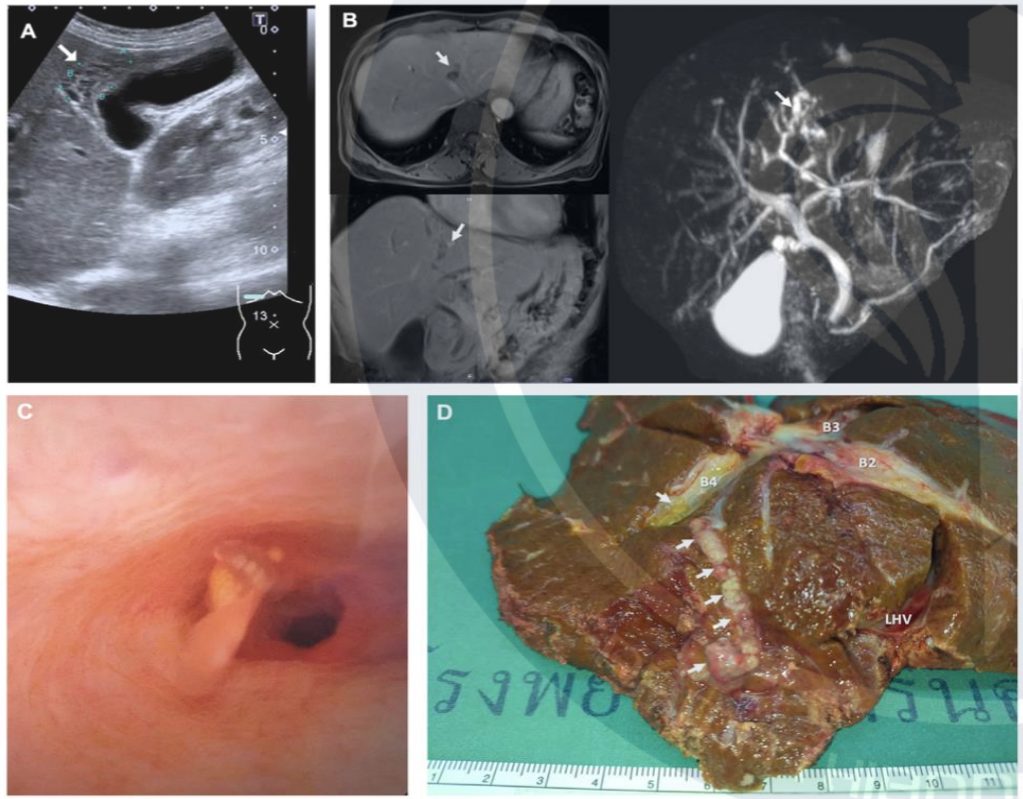
Gastro Hep Advances 2024;3:851–852

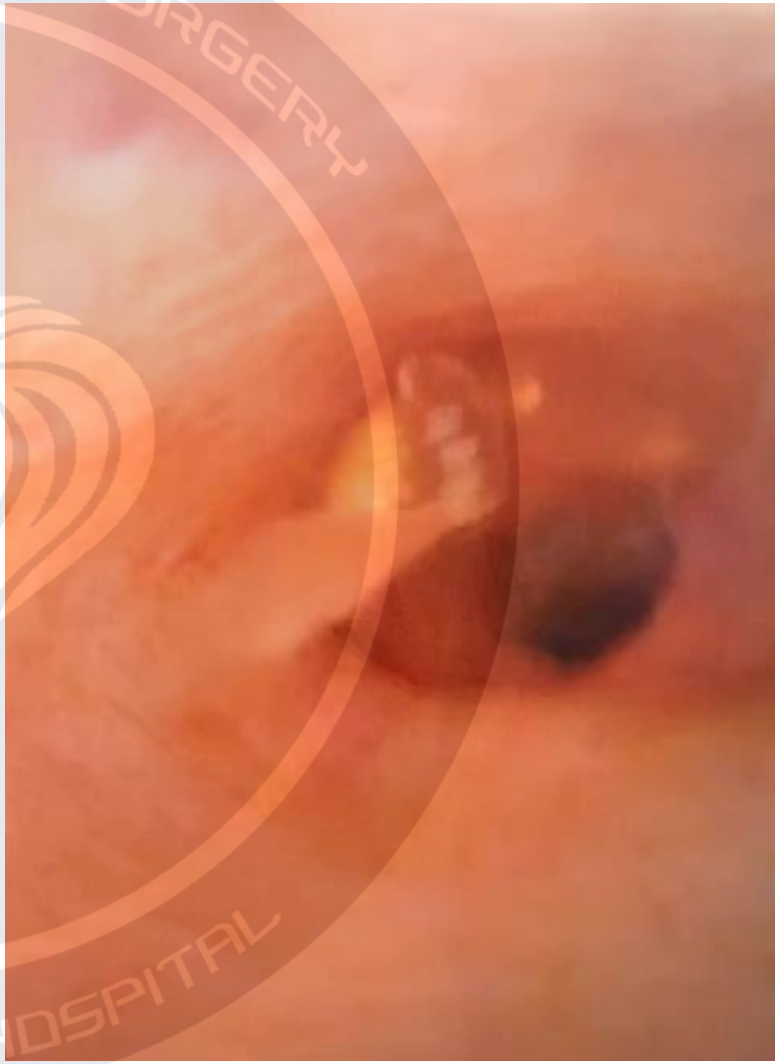
IMAGES OF THE MONTH

A Surprise in the Bile Duct

Ativitch Asavachaisuvikom, Pun Pugkhem, and Vor Luvira

Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand





Asavachaisuvikom A, Pugkhem P, Luvira V. A Surprise in the Bile Duct. Gastro Hep Adv. 2024 Jun 14;3(6):851-852. doi: 10.1016/j.gastha.2024.06.001. PMID: 39280923; PMCID: PMC11401542.

Intraductal papillary neoplasm of bile duct tumor (IPNB): Ativitch Asavachaisuvikom, MD. (F)

Epidemiology

- Prevalence of 4% to 15% among bile duct tumors
- IPNB was mainly reported in East Asia
- Major risk factor
  - Asian : Hepatolithiasis and liver fluke infection (Clonorchiasis sinensis or Opisthorchis viverrini infection)
  - Western : primary sclerosing cholangitis (PSC) and congenital biliary tract disease

Nakanuma Y, Uesaka K, Kakuda Y, Sugino T, Kubota K, Furukawa T, Fukumura Y, Isayama H, Terada T. Intraductal Papillary Neoplasm of Bile Duct: Updated Clinicopathological Characteristics and Molecular and Genetic Alterations. J Clin Med. 2020 Dec; 9(12): 3991. doi: 10.3390/jcm9123991. PMID: 33317146; PMCID: PMC7763595.

Imaging and Endoscopy

- Ultrasonography
  - hyperechoic nodules (37.5%)
  - focal bile duct dilatation (37.5%)
  - diffuse bile duct dilatation with intraductal nodules (25%)

Siripongsakun S., Sapthanakorn W., Mekraksakit P., Vichitpunt S., Chonyuen S., Seetasarn J., Bhumiwat S., Sricharunrat T., Srittanapong S. Preoperative evaluation of intraductal papillary neoplasm of bile duct tumor (IPNB) using computed tomography and MRI: Characteristics on ultrasonography and MRI. Abdom. Radiol. 2019;44:2133–2146

Imaging and Endoscopy

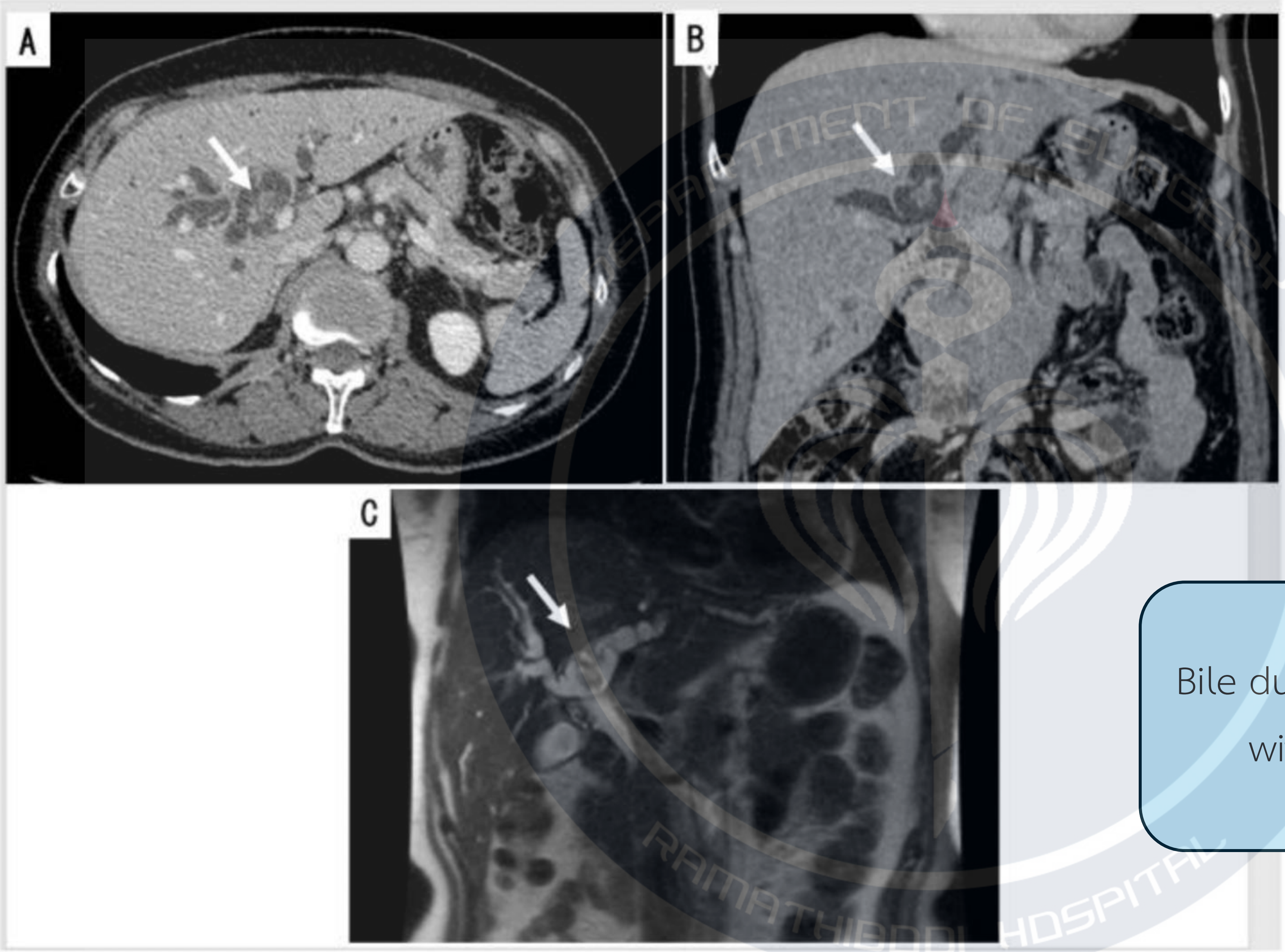
- Cross sectional imaging

    (a) intraductal mass(es) and surrounding intraepithelial neoplastic biliary mucosa

    (b) diffuse or segmental bile duct dilatation with or without cystic changes (maximum 126 mm)

    (c) ductal and periductal invasion including macro-invasion of the liver

Aslam A., Wasnik A.P., Shi J., Sahai V., Mendiratta-Lala M. Intraductal papillary neoplasm of the bile duct (IPNB): CT and MRI appearance with radiology-pathology correlation. Clin. Imaging 2020;66:10–17.

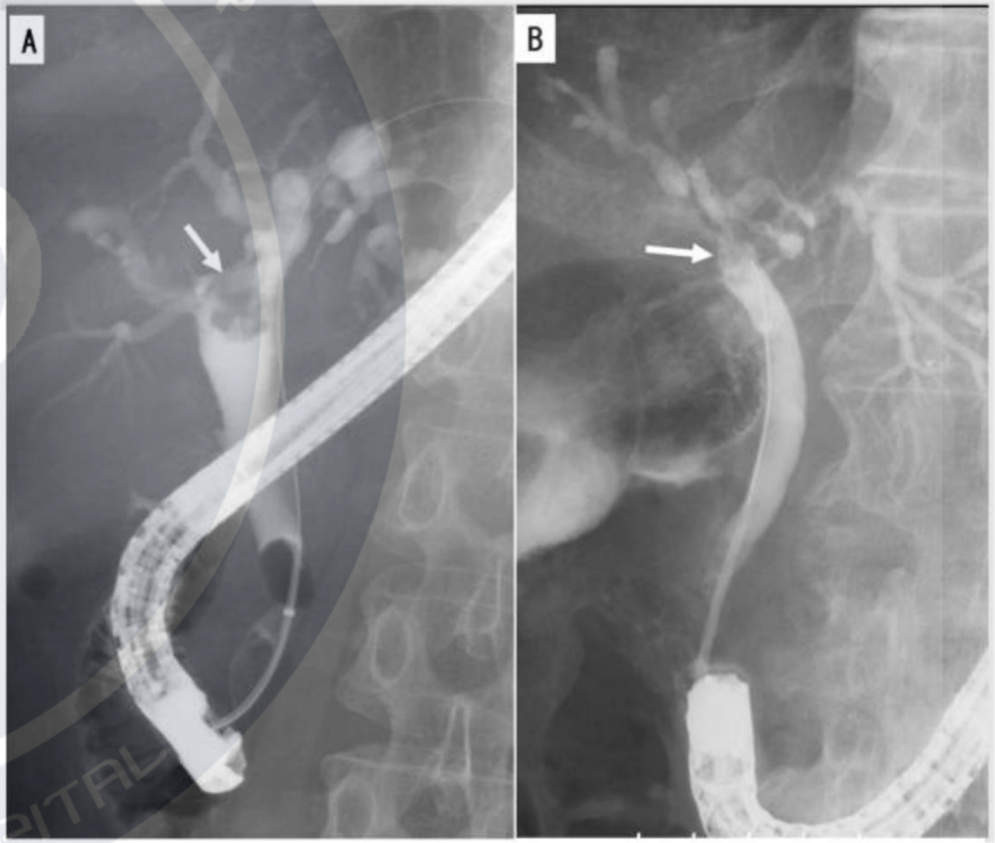


Bile duct reveals diffuse dilatation with low intensity tumors

Aslam A., Wasnik A.P., Shi J., Sahai V., Mendiratta-Lala M. Intraductal papillary neoplasm of the bile duct (IPNB): CT and MRI appearance with radiology-pathology correlation. Clin. Imaging 2020;66:10–17.

Imaging and Endoscopy

- ERCP
  - Useful for detecting mucobilia
  - Diffuse dilatation of the bile duct with an irregular or amorphous filling defect



Tsuyuguchi T., Sakai Y., Sugiyama H., Miyakawa K., Ishihara T., Ohtsuka M., Miyazaki M., Yokosuka O. Endoscopic diagnosis of intraductal papillary mucinous neoplasm of the bile duct. Hepatobiliary Pancreat Sci. 2010;17:230–235. doi: 10.1007/s00534-009-0153-z.

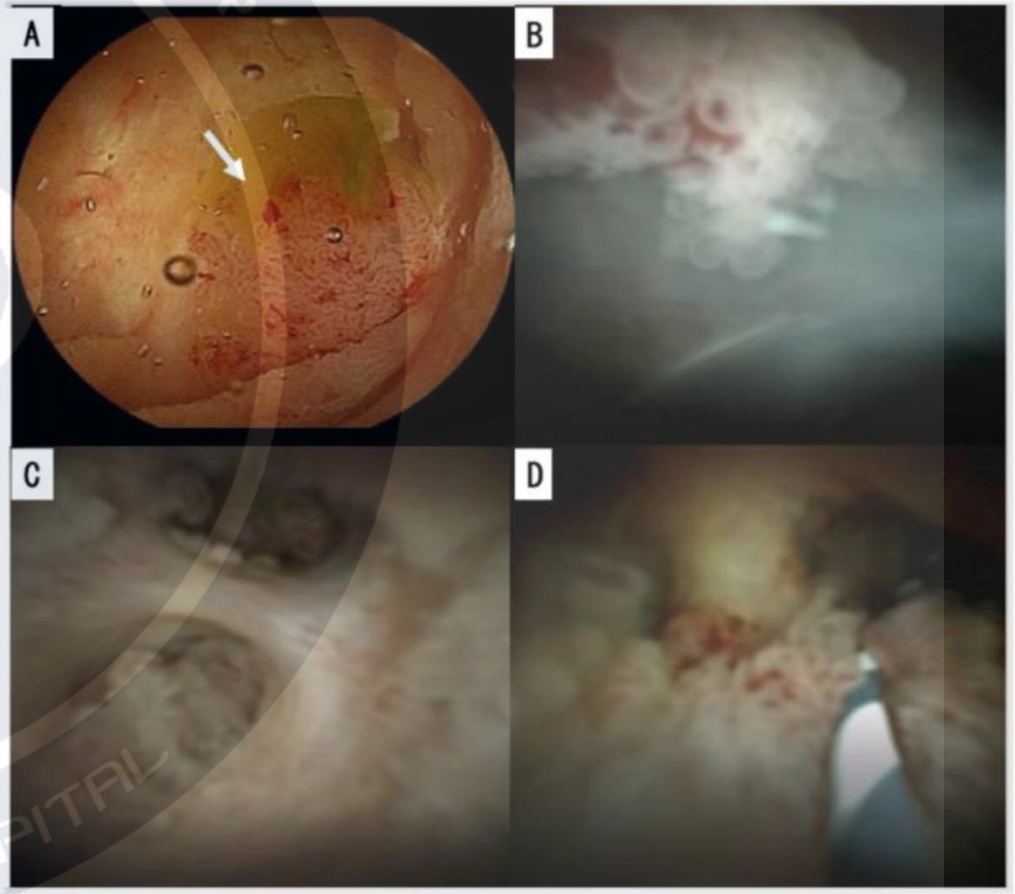
Imaging and Endoscopy

- Intraductal ultrasonography
  - location of IPNB and assessing the depth and extent of invasion
  - presence of thick mucin

Ito Y., Shibutani S., Egawa T., Hayashi S., Nagashima A., Kitagawa Y. Utility of intraductal ultrasonography as a diagnostic tool in patients with early distal cholangiocarcinoma. Hepatogastroenterology. 2015;62:782–786.

Imaging and Endoscopy

- Cholangioscopy and Duodenoscopy
  - Peroral cholangioscopy (POCS) can visualize the bile duct directly and assess the extent of the tumor
  - Direct cholangioscopy : direct visualization and diagnostic sampling



Itoi T., Sofuni A., Itokawa F., Tsuchiya T., Kurihara T., Ishii K., Tsuji S., Moriyasu F., Gotoda T. Peroral cholangioscopic diagnosis of biliary-tract diseases by using narrow-band imaging (with videos). Gastrointest Endosc. 2007;66:730–736. doi: 10.1016/j.gie.2007.02.056.

Histology and morphology subtype

Histology

- Four subtype
  - Intestinal type
  - Pancreatobiliary type
  - Oncocytic type
  - Gastric type

} Neoplastic epithelial lining

- Tumor grading
  - Low grade dysplasia
  - High grade dysplasia
  - Invasive

Nakanuma Y, Uesaka K, Kakuda Y, Sugino T, Kubota K, Furukawa T, Fukumura Y, Isayama H, Terada T. Intraductal Papillary Neoplasm of Bile Duct: Updated Clinicopathological Characteristics and Molecular and Genetic Alterations. J Clin Med. 2020 Dec 9;9(12):3991.

Table 3. Characteristics of four subtypes of intraductal papillary neoplasm of bile duct (IPNB).

Four Subtypes	Definitions	Immunohistochemistry
Intestinal subtype	* Neoplastic epithelia lining the fibrovascular cores showing columnar cells with pseudostratified, cigar-shaped nuclei and basophilic or amphophilic cytoplasm and with variable amounts of supranuclear mucin, resembling colorectal neoplasms. * Presenting mainly villous structures, papillovillous or mixed papillotubular or tubular patterns reminiscent of tubular or villotubular neoplasms of the colorectum.	* Positive for CK20 and/or * CDX2 in their cytoplasm * Positive for MUC2 in goblet cells
Gastric subtype	* Neoplastic lining composed of tall columnar cells with basally oriented nuclei and abundant pale mucinous cytoplasm, reminiscent of the gastric foveolar epithelium, intermingling with glandular areas reminiscent of gastric pyloric glands. * High-grade dysplasia showing columnar epithelia with more complicated structures including irregular papillary or tubular or microcystic changes with atypical features.	* Positive for MUC5AC in the foveolar areas and for MUC6 in the pyloric gland portions.
Pancreatobiliary subtype	* Ramifying fine and thin branches and papillae covered by cuboidal to low columnar epithelia with acidophilic or amphophilic or pale cytoplasm, and by a less mucinous appearance * Round, hyperchromatic nuclei, prominent nucleoli * Including the cases with irregular papillary architecture with more stratified nuclei and solid or comedo-like structures with atypical structures and cells and nuclei.	* Positive for S100P and MUC1 and negative for MUC5AC.
Onocytic subtype	* Complex and arborizing papillae with delicate fibrotic and edematous stroma, lined by one to several stratified layers of cuboidal to columnar cells with abundant eosinophilic granular cytoplasm and occasional hyaline globules * Hyperchromatic, round, large, and fairly uniform nuclei * Frequent secondary intraepithelial lumina.	* Positive for MUC5AC.

CK, cytokeratin; MUC, mucus core protein. *, main features of each subtype are itemized.

A stateme … or future clinicopat … nsensus building o … duct through s…

Yasuni Nakanum… ng. Ha…

Fir…

	Type 1 IPNB (classical IPNB)	Type 2 IPNB (so-called papillary carcinoma or cholangiocarcinoma)
Location	Commonly intrahepatic bile ducts	Typically extrahepatic bile ducts including hilar ducts
Gross mucin	Common (approximately 80%)	Rare (approximately 10%)
Histological architecture	Well organized papillary growth with thin fibrovascular stalks.	Complex papillary growth with thick papillae or irregular branching with fine
Low/intermediate-dysplasia component	Frequent (approximately 20%)	Occasional
Associated invasive cancer	Approximately 50%	>90%

PRO : reached the common understanding

CONS : some cases may have overlapping features(extensive disease)

Not guided management

Pathologic patterns of invasive carcinoma associated with intraductal papillary neoplasms of bile duct (IPNB)

Yasuni Nakanuma [a,c,*], Takashi Sugino [a], Yuko Kakuda [a], Yukiyasu Okamura [b,d], Katsuhiko Uesaka [b], Yoshikatsu Nomura [e], Hiroyuki Watanabe [e], Takuro Terada [f], Yuki Fukumura [g], Yoshifumi Ohnishi [h], Yasunori Sato [i]

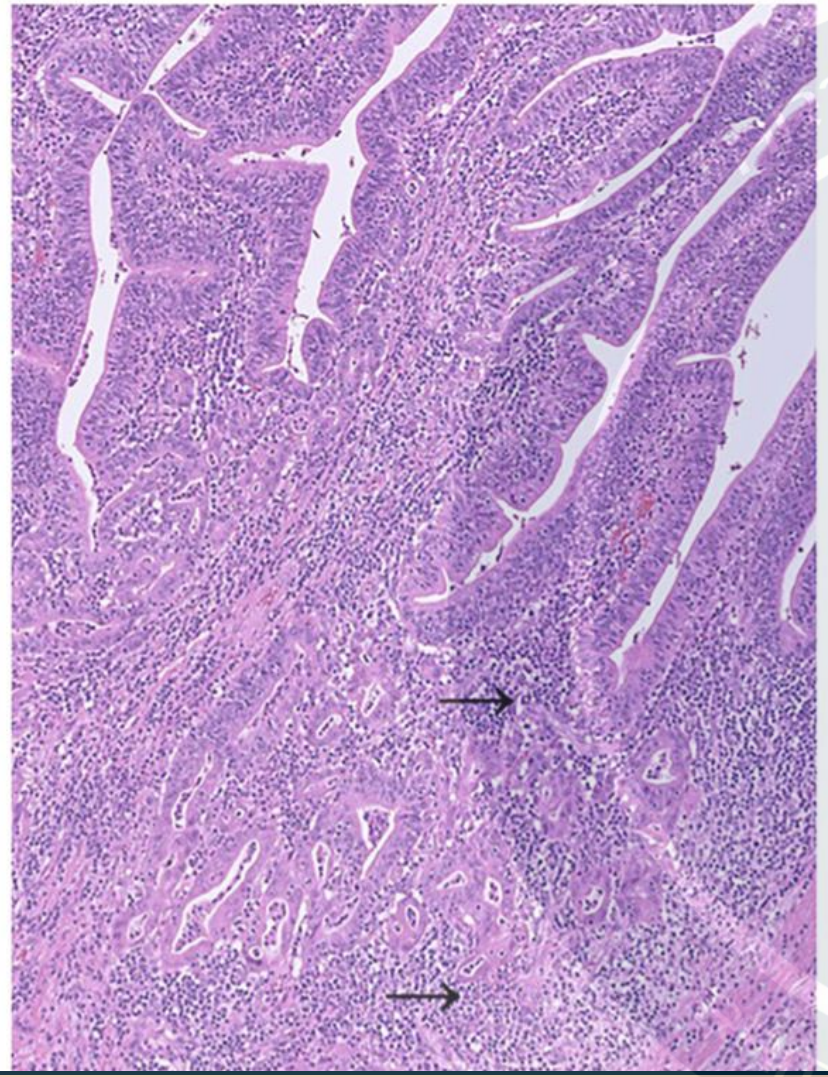
Pattern A : Focal or multiple microscopic foci of invasive carcinoma in the fibrovascular stalks and in the bile duct mucosa and within the wall beneath of the intraluminal components of IPNB

Pattern B : Invasive carcinomas were found in the periductal loose connective tissue outside the bile duct wall and surrounding organs mainly near the intraluminal papillary component(s) of IPNB and their sizes were variable

Pattern C : This pattern was characterized by sizable, considerable sized invasive carcinoma involving the intraductal preinvasive papillary neoplasm or in the bile duct wall and mucosa adjacent to preinvasive intraepithelial components of IPNB

Yasuni Nakanuma, Takashi Sugino, Yuko Kakuda. Pathologic patterns of invasive carcinoma associated with intraductal papillary neoplasms of bile duct (IPNB), Annals of Diagnostic Pathology, Volume 61, 2022

A

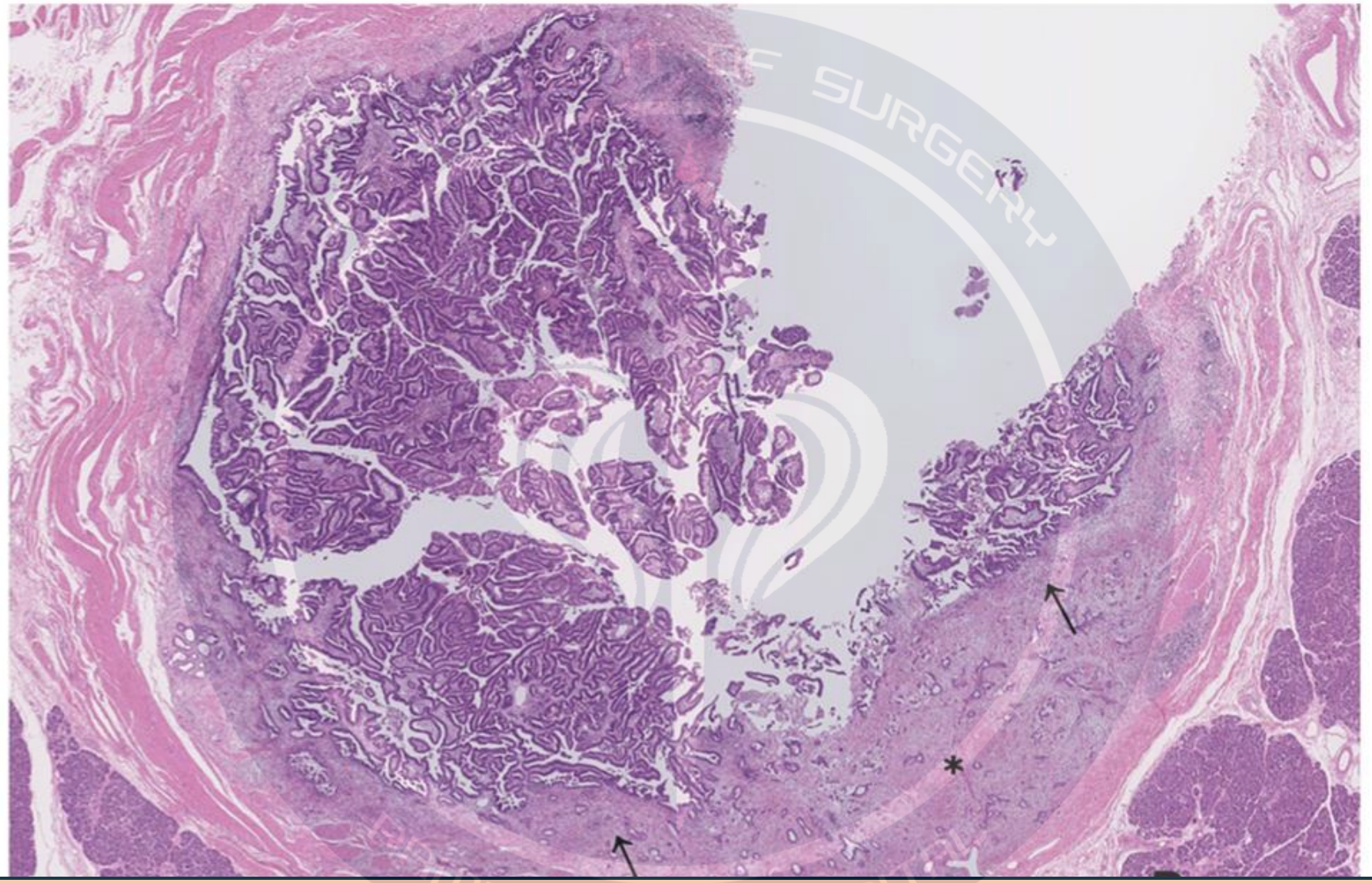


B

Foci of invasion within fibrovascular stalk

Invasive carcinoma is found in the periductal connective tissue and hepatic parenchyma (arrows)

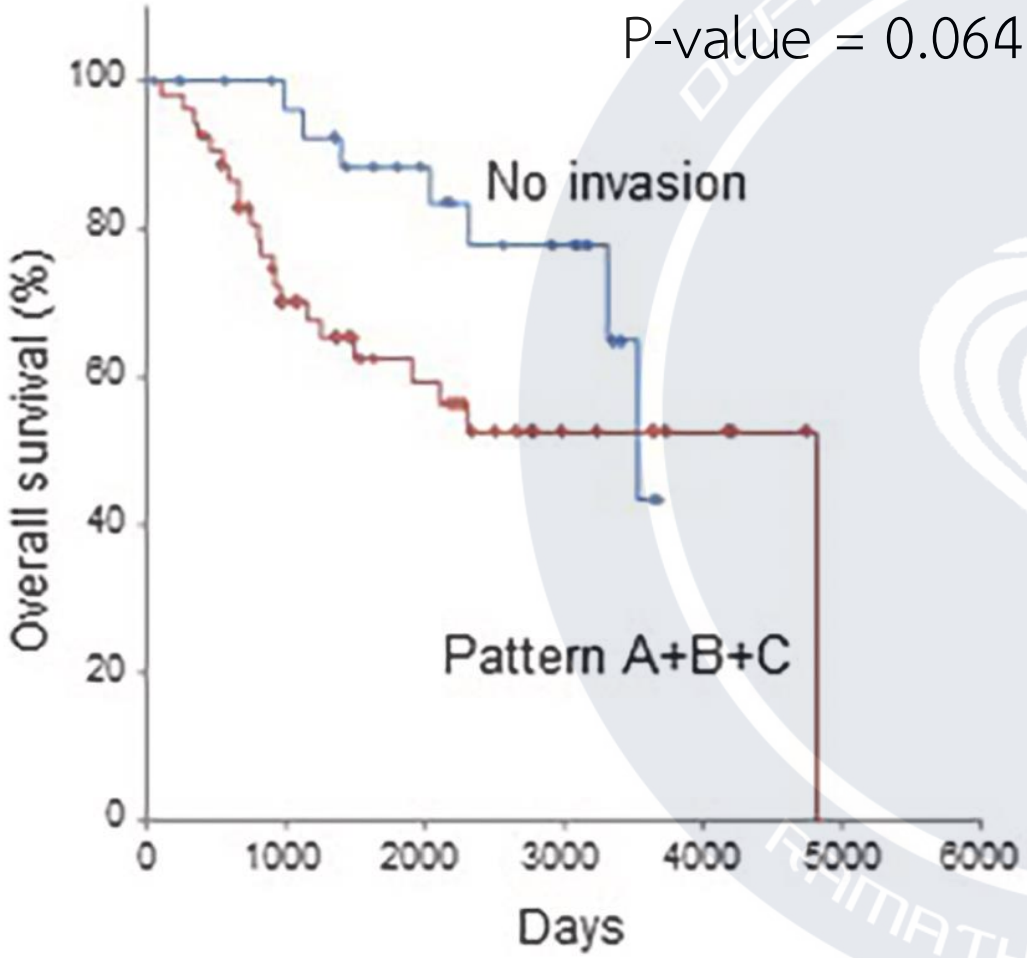
C



Nodular invasive carcinoma (*) with desmoplastic reaction involving the bile duct wall adjacent to intraductal papillary preinvasive neoplasm of bile duct (IPNB)

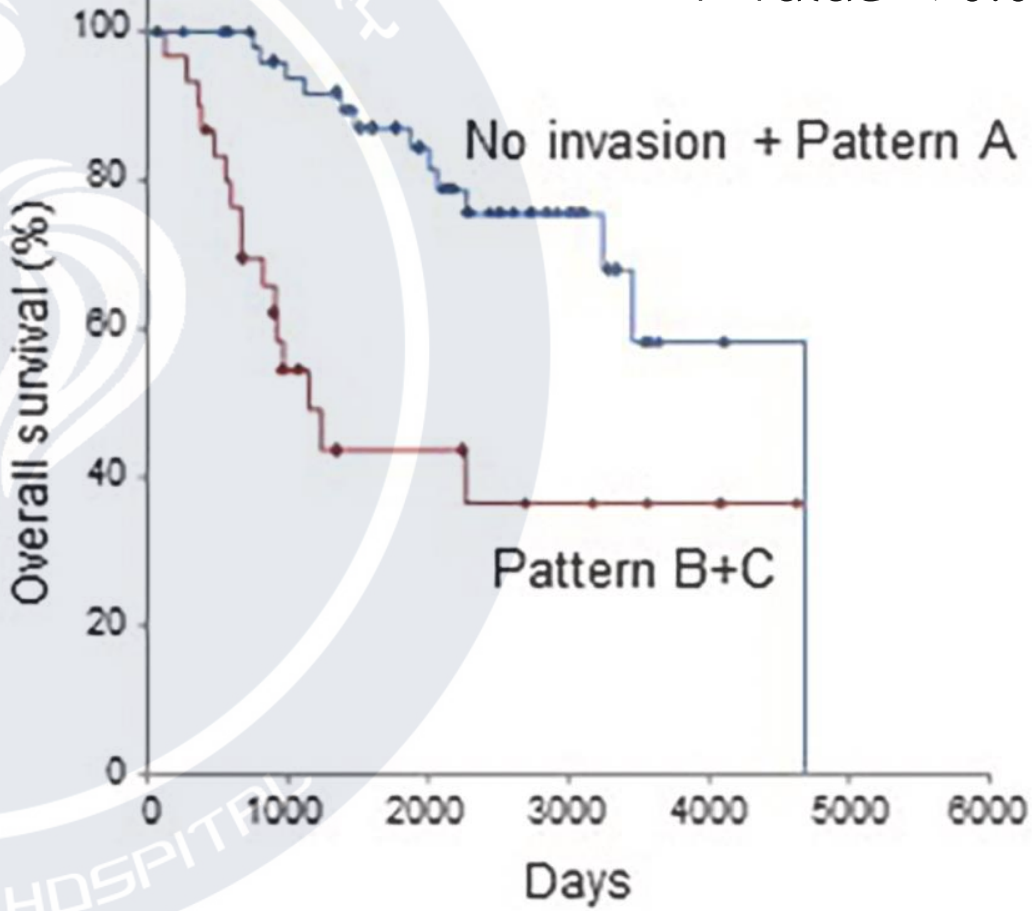
No invasion vs. Pattern A+B+C

P-value = 0.064



No invasion + Pattern A vs. Pattern B+C

P-value < 0.001



RESEARCH ARTICLE

Morphological Classification of Intraductal Papillary Neoplasm of the Bile Duct with Survival Correlation

Vor Luvira[1]*, Kulyada Somsap[2], Ake Pugkhem[1], Chalerm Eurboonyanun[1], Varisara Luvira[3], Vajarabhongsa Bhudhisawasdi[1], Chawalit Pairojkul[4], Supot Kamsa Ard[5]

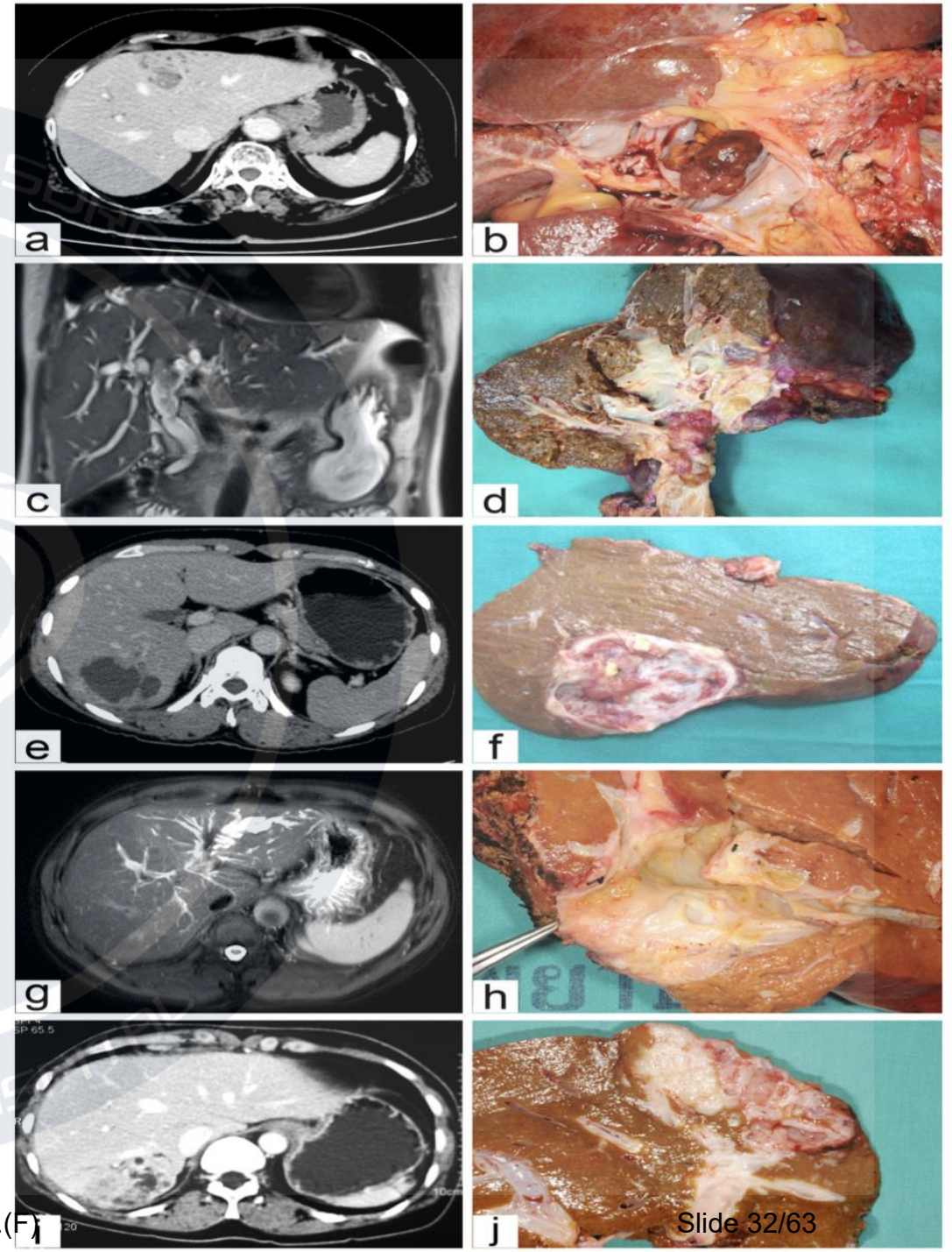
Class I – Classical intrahepatic IPNB (i.e., presence of an intraductal tumor with unilateral intrahepatic duct dilatation)

Class II – Extrahepatic IPNB (i.e., presence of an intraductal tumor with bilateral intrahepatic duct dilatation)

Class III – Cystic variant (i.e., cystic tumor with a papillary tumor inside and the presence of bile duct communication)

Class IV – Micro-papillary lesion (i.e., disproportional bile duct dilatation in the absence of any discernible tumor)

Class V – Macroinvasion (i.e., presence of a mass-forming tumor incorporate with intraductal tumor)

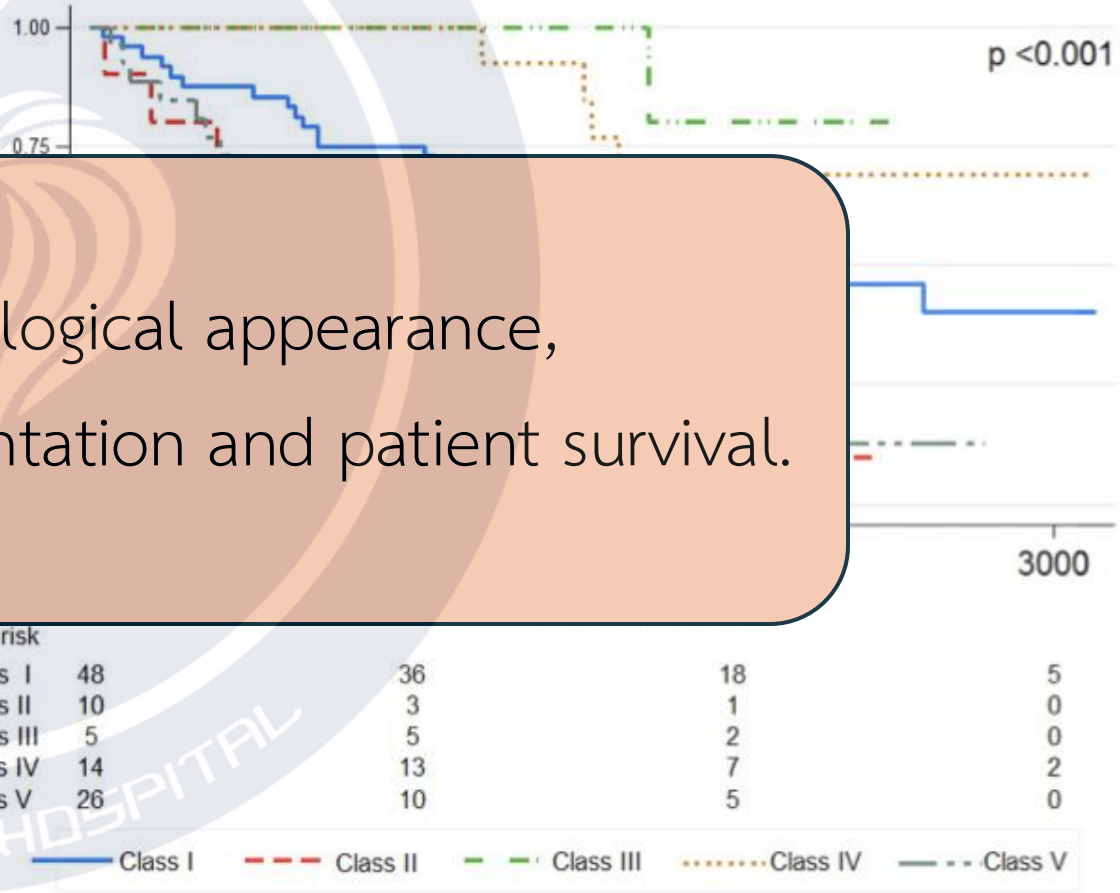


RESEARCH ARTICLE

Morphological Classification of Intraductal Papillary Neoplasm of the Bile Duct with Survival Correlation

Vor Luvira[1]*, Kulyada Somsap[2], Ake Pugkhem[1], Chalerm Eurboonyanun[1], Varisara Luvira[3], Vajarabhongsa Bhudhisawasdi[1], Chawalit Pairojkul[4], Supot Kamsa Ard[5]

Factors	Crude HR	Adjusted HR (95%CI)	p
Class of IPN			
I			
II			
III			
IV			
V			
Level of inv			
Benign IPNB	1.0	1	
Malignant IPNB	3.2	1.5 (0.4- 5.3)	
Lymph node metastasis			0.005
No	1.0	1	
Yes	3.4	2.7 (1.4-5.2)	



Based on its radio-pathological appearance,

correlated with its clinical presentation and patient survival.

Luvira, V., Somsap, K., Pugkhem, A. Morphological Classification of Intraductal Papillary Neoplasm of the Bile Duct with Survival Correlation. Asian Pacific Journal of Cancer Prevention, 2017; 18(1): 207-213.

Management

Preoperative tissue diagnosis

- Procedure
  - ERCP with brush cytology
  - EUS with FNA
  - Percutaneous cholangioscopy “ → Tumor seeding 1.7 – 5.2%
  - Peroral cholangioscopy
  - Spyglass cholangiopancreatography

Controversy

Huang XH, [illegible] Type 1 and Type 2 Intraductal Papillary Neoplasms of the Bile Duct. Curr Med Sci. 2024 Jun;44(3):485-493. doi: 10.1007/s11596-024-2863-5. Epub 2024 May 15. PMID: 38748369.

Surgical planning

- Patient factor
  - Performance status, Underlying disease
- Liver factor
  - Liver function, Liver volume
- Disease factor
  - Role of preoperative biliary drainage
  - Margin status
  - Role of lymphadenectomy
  - Extensive disease/Bilobar lesion

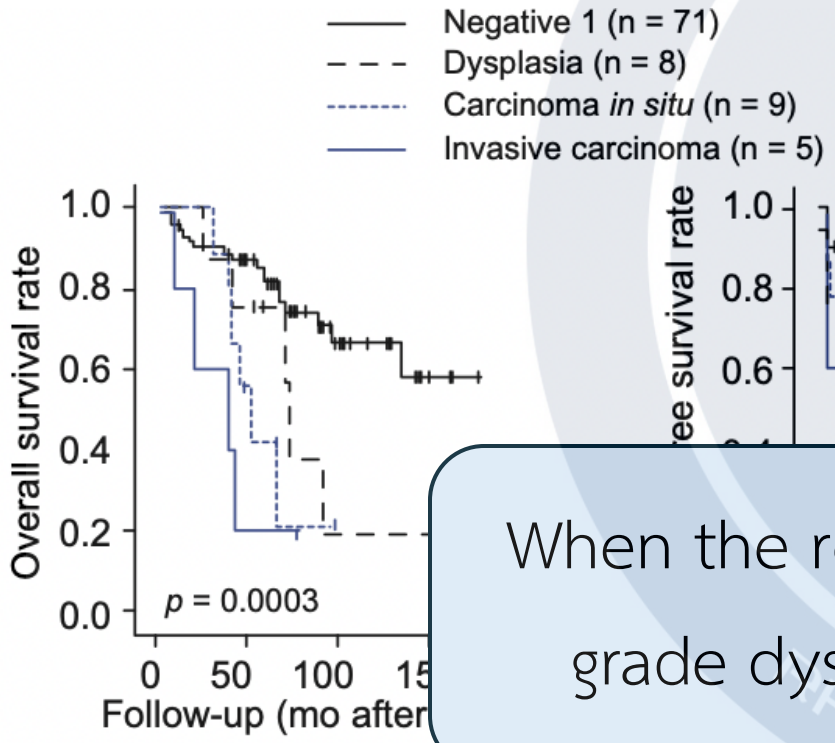
Preoperative biliary drainage

- Preoperative biliary drainage is recommended, especially for cases in which extended liver resection (hemihepatectomy or trisectionectomy) is required.
- Indication
  - Obstructive jaundice
  - Cholangitis
- Route
  - Prefer endoscopic transpapillary route

Nagino M, Hirano S, Yoshitomi H, Aoki T, Uesaka K, Unno M, Ebata T, Konishi M, Sano K, Shimada K, Shimizu H, Higuchi R, Wakai T, Isayama H, Okusaka T, Tsuyuguchi T, Hirooka Y, Furuse J, Maguchi H, Suzuki K, Yamazaki H, Kijima H, Yanagisawa A, Yoshida M, Yokoyama Y, Mizuno T, Endo I. Clinical practice guidelines for the management of biliary tract cancers 2019: The 3rd English edition. J Hepatobiliary Pancreat Sci. 2021 Jan;28(1):26-54. doi: 10.1002/jhbp.870. Epub 2020 Dec 23. PMID: 33259690.

Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

Margin status



A Retrospective review

93 non-invasive and invasive IPNB cases,

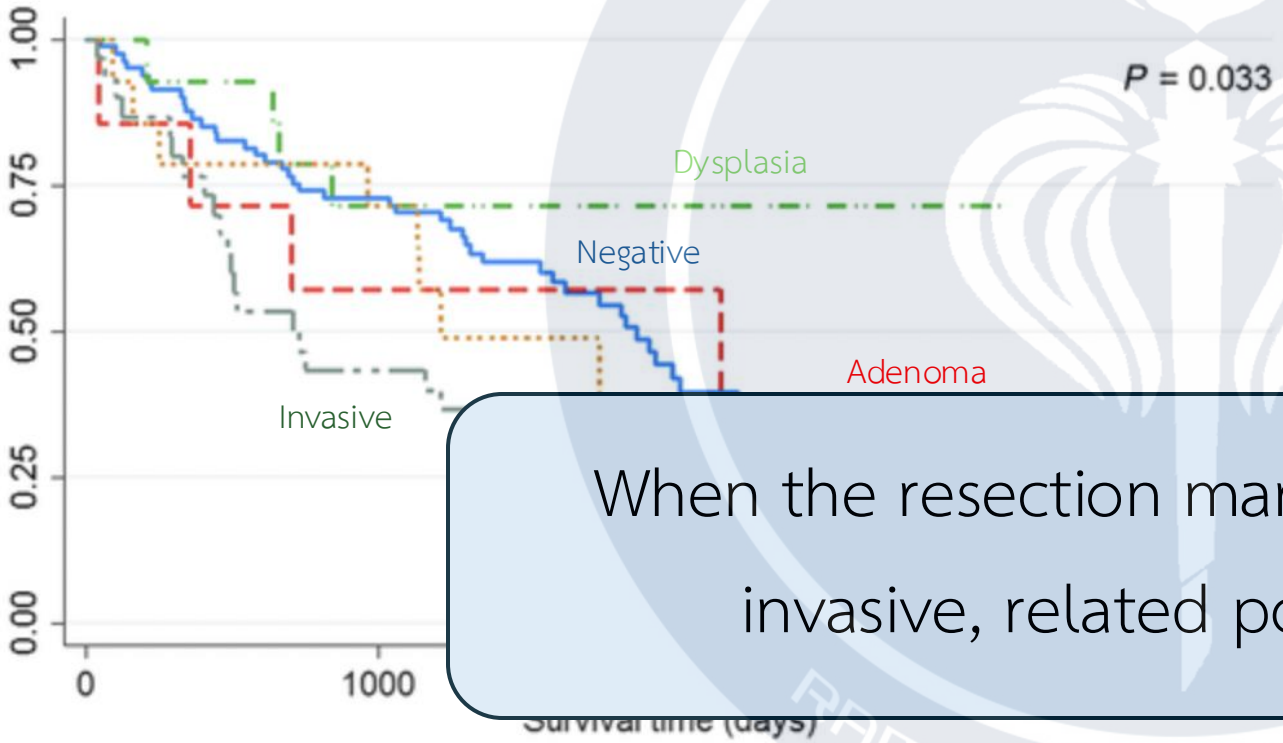
surgically resected from 1996 to 2006

Asan medical center

When the resection margin is involved by high grade dysplasia, consider radical resection

Jung G, Park KM, Lee SS, Yu E, Hong SM, Kim J. Long-term clinical outcome of the surgically resected intraductal papillary neoplasm of the bile duct according to histologic grade and type. J Hepatol. 2012 Oct;57(4):787-93. doi: 10.1016/j.jhep.2012.05.008. Epub 2012 May 23. PMID: 22634127.

Margin status



A Retrospective review

149 IPNB case

surgically resected from 2005 to 2011

When the resection margin is involved by invasive, related poor outcome

Luvira V, Pugkhem A, Bhudhisawasdi V, Pairojkul C, Sathitkarnmanee E, Luvira V, Kamsa-Ard S. Long-term outcome of surgical resection for intraductal papillary neoplasm of the bile duct. J Gastroenterol Hepatol. 2017 Feb;32(2):527-533. doi: 10.1111/jgh.13531. PMID: 27356284.

ABSTRACT ONLY · Volume 26, Supplement 3, S846, 2024

Impact of intraoperative cholangioscopy on survival of the patients with intraductal bile duct tumor

Dr Ativitch Asavachaisuvikom, MD · Vor Luvira, MD FRCST · Dr Chalisa Suwanprinya, MD · ... · Dr Ake Pugkhem, MD FRCST · Chawalit Pairojkul, MD · Vajarabhongsa Bhudhisawasdi, MD FRCST
... Show more

	Non scope (n=230)	Scope (n=30)	P value
Margin status			0.397
Free	159 (69.1%)	23 (76.7%)	
Adenoma	3 (1.31%)	1 (3.3%)	
dysplasia	9 (3.93%)	2 (6.7%)	
CIS	4 (1.75%)	1 (3.3%)	
Invasive	55 (24.0%)	3 (10%)	

Rate of presence of invasive foci on surgical margin seemed to be lower in scope group compared to non-scope group (10% vs. 24%, p-value = 0.085)

unpublished, KKU

ABSTRACT ONLY · Volume 26, Supplement 3, S846, 2024

Impact of intraoperative cholangioscopy on survival of the patients with intraductal bile duct tumor

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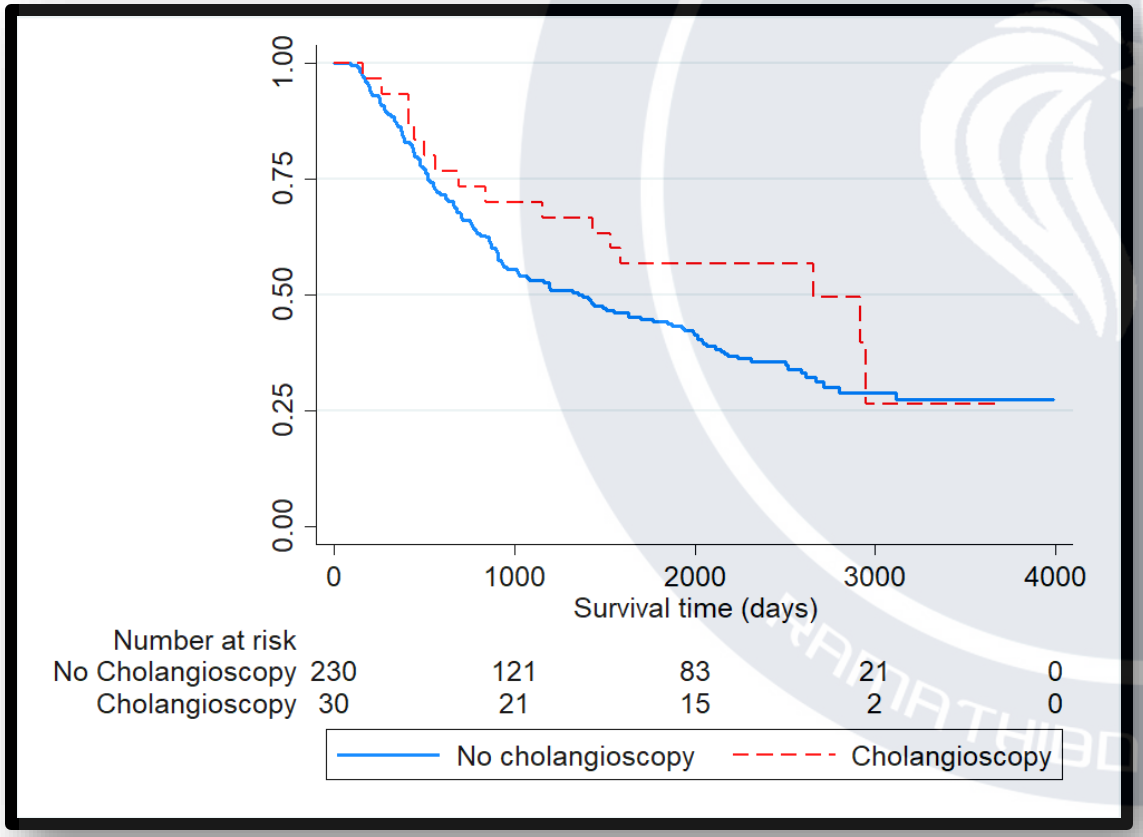
... Show more



Median OS

Scope 88.5 mo, Non scope 45 mo

(p-value = 0.125)

The 1, 3 and 5 years overall survival rate

- scope group 93.3%, 70% and 56.7%
- non-scope group 86.2%, 53.2% and 44.3%

Intraductal papillary neoplasm of bile duct tumor (IPNB): Ativitch Asavachaisuvikom,MD.(F)

unpublished, KKU

Lymphadenectomy

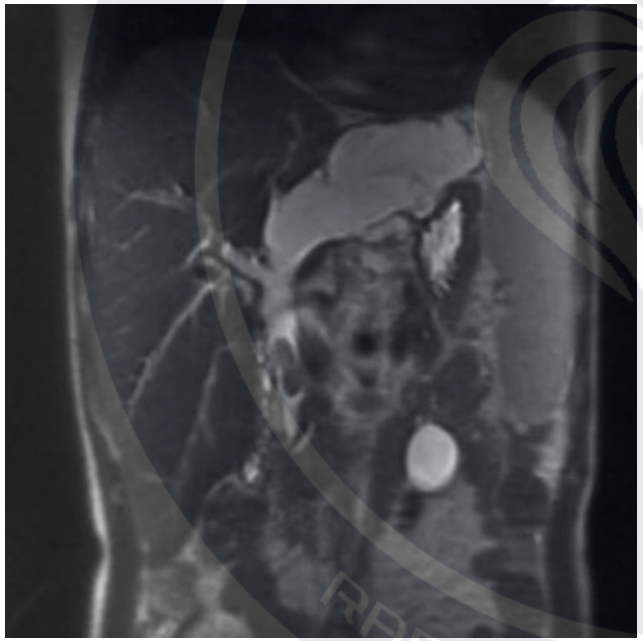
- Nodal metastasis 11 - 15%
- Recommend for routine lymphadenectomy
- But may be omitted in Cystic type IPNB[2]

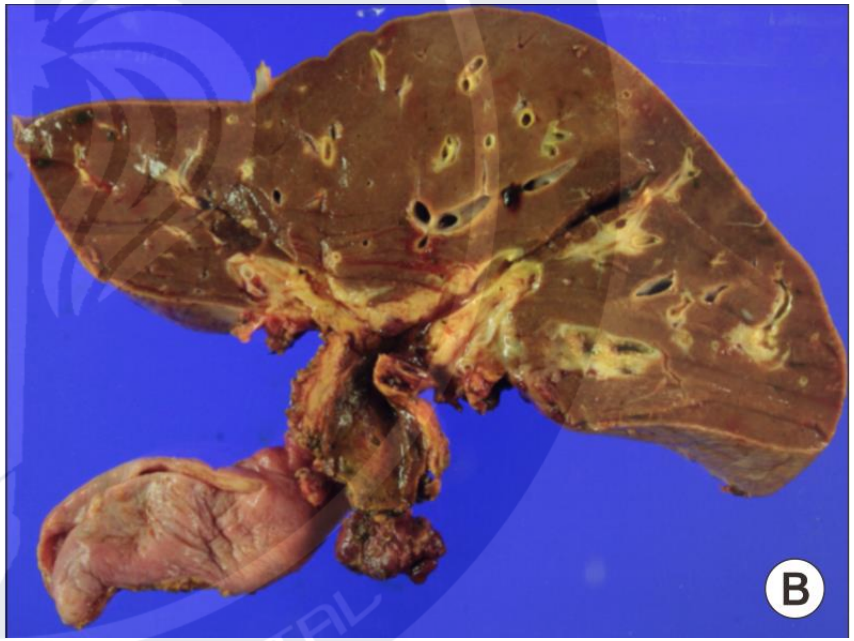
Jung G, Park KM, Lee SS, Yu E, Hong SM, Kim J. Long-term clinical outcome of the surgically resected intraductal papillary neoplasm of the bile duct. J Hepatol. 2012 Oct;57(4):787-93. doi: 10.1016/j.jhep.2012.05.008. Epub 2012 May 23. PMID: 22634127.

Luvira V, Somsap K, Pugkhem A, Eurboonyanun Ch, Luvira V, Bhudhisawasdi V, Pairojkul Ch, Kamsa Ard S. Morphological Classification of Intraductal Papillary Neoplasm of the Bile Duct with Survival Correlation. Asian Pac J Cancer Prev. 2017 Jan 1;18(1):207-213.

Extensive disease

- Insufficient data but may be indicate for liver transplant(case report)





Choi JU, Hwang S, Jung DH, Park GC, Ahn CS, Kim KH, et al. Living donor liver transplantation for diffuse biliary papillomatosis with malignant change: A case report with 10-year follow-up. Ann Hepatobiliary Pancreat Surg. 2020;24:209–15.

Lessard J, Sauvé C, Dagenais M, Vincent C. Extensive high-grade intraductal papillary neoplasm: what is the optimal treatment strategy? Liver Transpl. 2012;18:1259–60.

Post operative outcome

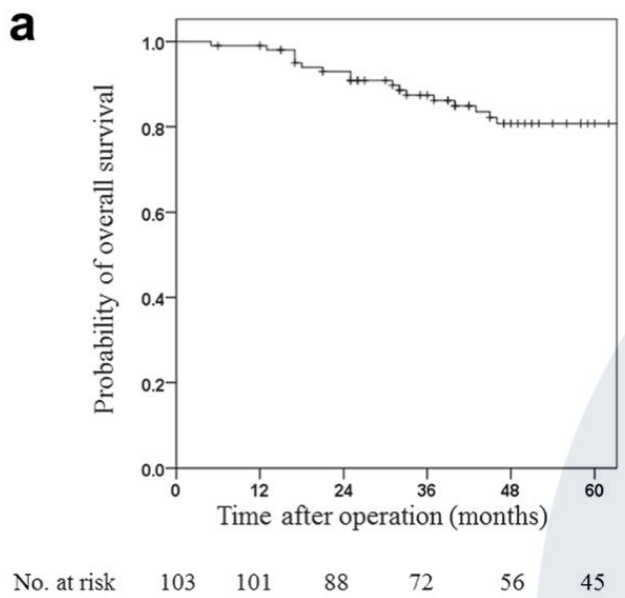
Journal of Gastrointestinal Surgery
https://doi.org/10.1007/s11605-019-04235-8

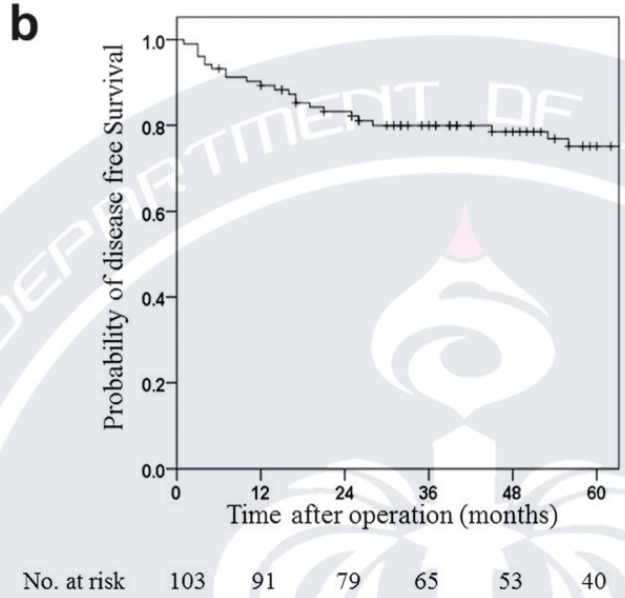
ORIGINAL ARTICLE

Recurrence After Resection for Intraductal Papillary Neoplasm of Bile Duct (IPNB) According to Tumor Location

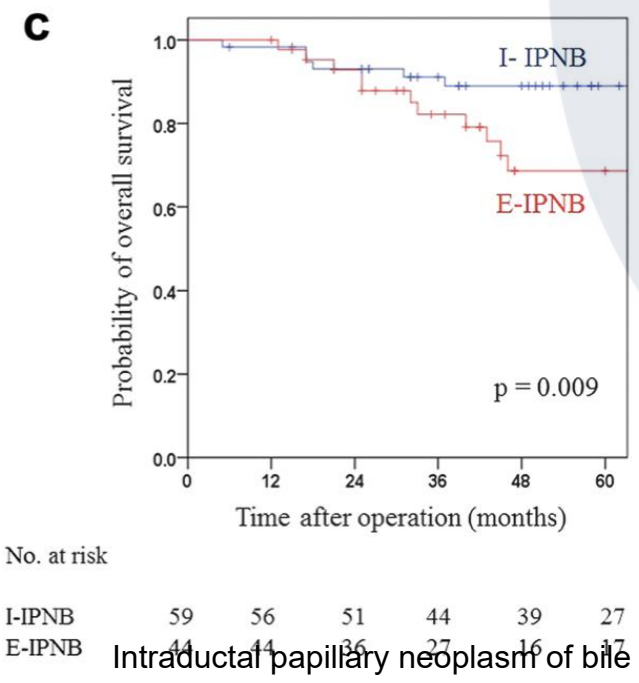
Yunghun You[1] · Seong Ho Choi[2] · Dong Wook Choi[3] · Jin Seok Heo[3] · In Woong Han[3] · Kee-Taek Jang[4] · Sunjong Han[5]

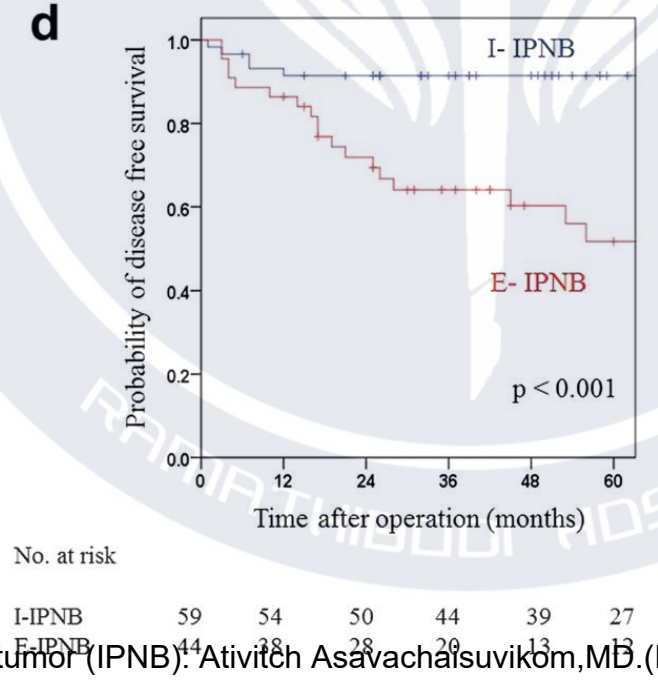
- 103 patients who diagnosed IPNB, retrospectively reviewed
- Multicenter in South Korea
- F/U q 3 months until 12 months, then every 6 months
- **The 5-year overall survival (OSR) and disease-free survival (DFS)** rates of all 103 cases were **80.8% and 75.2%,** respectively



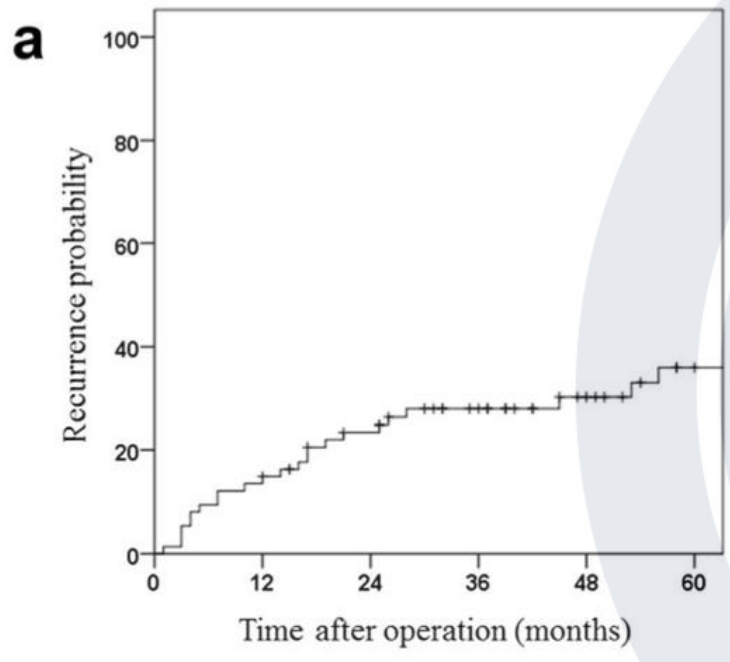


Recurrence rate according to timing was different between E-IPNB and I-IPNB: within 1 year (33.3% vs. 83.3%; p = 0.061) and 1–3 years (50.0% vs. 0%; p = 0.052).

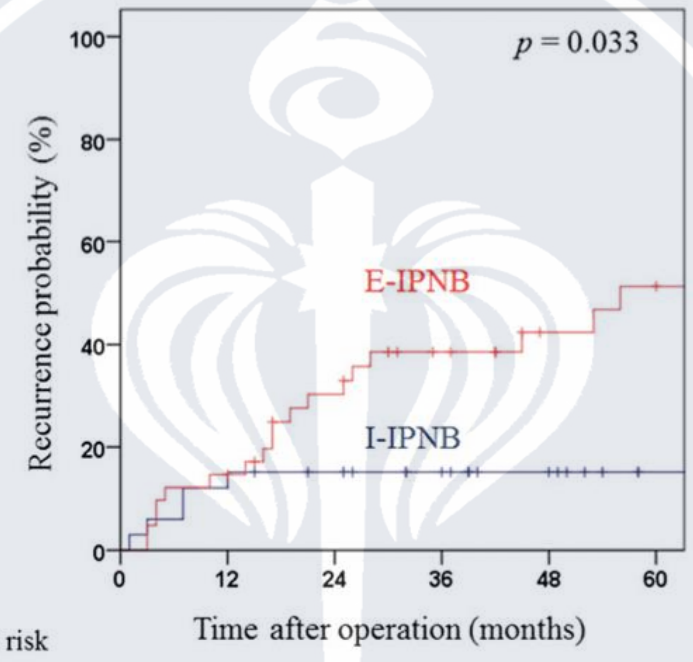




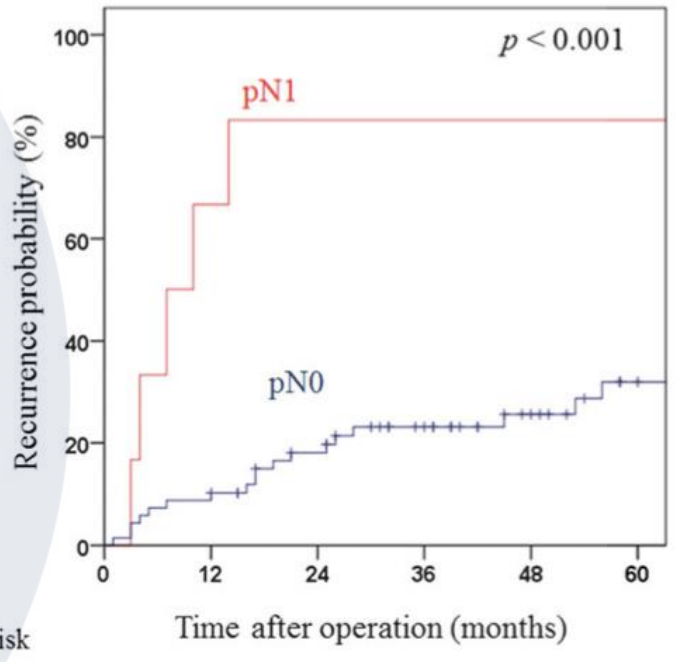
E-IPNB has poorer 5-year recurrence-free survival (RFS) **compared to I-IPNB** (51.7 vs. 91.4%; p < 0.001)



No. at risk						
No. at risk	74	63	51	39	28	19



No. at risk						
I-IPNB	33	28	25	20	15	8
E-IPNB	41	34	25	18	12	10



No. at risk						
pN0	68	61	50	38	27	18
pN1	6	2	1	1	1	1

World Journal of Surgery

Original Scientific Report | Full Access

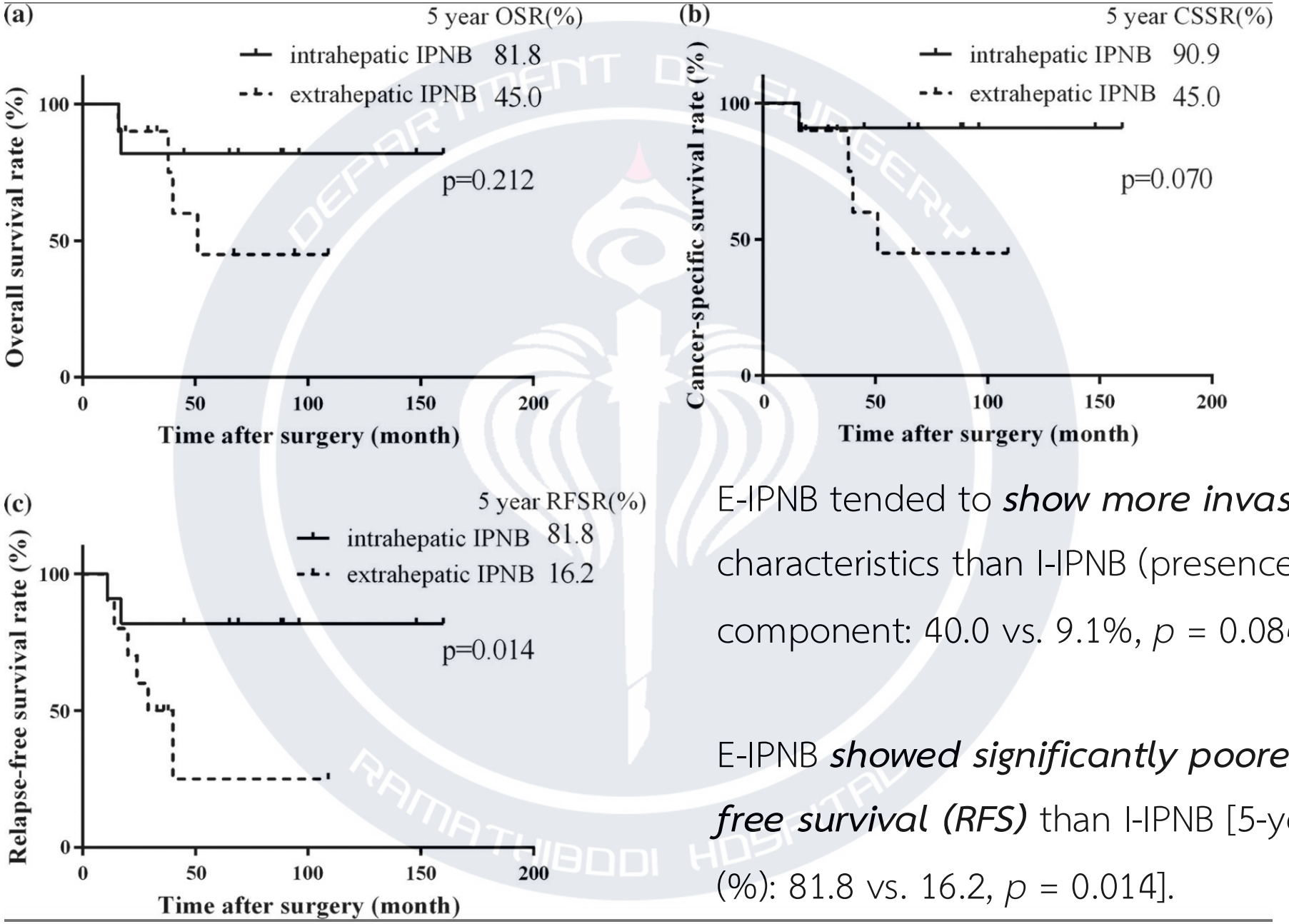
Impact of Tumor Location on Postoperative Outcome of Intraductal Papillary Neoplasm of the Bile Duct

Takatsugu Matsumoto ✉, Keiichi Kubota, Hiroyuki Hachiya, Yuhki Sakuraoka, Takayuki Shiraki, Takayuki Shimizu, Shozo Mori, Yukihiro Iso, Masato Kato, Hidetsugu Yamagishi, Yasuo Imai, Taku Aoki

First published: 18 January 2019 | https://doi.org/10.1007/s00268-019-04913-3 | Citations: 1

306 patients who underwent surgical resection with a diagnosis of bile duct tumor

21 patients were diagnosed IPNB



E-IPNB tended to ***show more invasive*** characteristics than I-IPNB (presence of invasive component: 40.0 vs. 9.1%, p = 0.084).

E-IPNB ***showed significantly poorer relapse-free survival (RFS)*** than I-IPNB [5-year RFS rate (%): 81.8 vs. 16.2, p = 0.014].

Systematic Review and Meta-analysis of Current Experience in Treating IPNB

Clinical and Pathological Correlates

Alex N. Gordon-Weeks, MBChB, BSc, MRCS, DPhil, Keaton Jones, MRCS,† Elinor Harriss, MSc, MA,‡ Adrian Smith, MBBS, DPhil,§ and Michael Silva, MBBS, MD, MS, FRCS (Gen), FRCS Ed¶*

ANNALS OF SURGERY

TABLE 3. Relationship Bet

					Total Patients (%)
Possible etiological associatio				0)	40 (27.6)
				0)	35 (21.2)
Tumor position				4.4)	70 (44.3)
Tumor grade				8.5)	101 (35.7)
Tumor antigens				71.4)	124
				57.1)	124
				91.7)	105
				50.0)	92
				4/6 (66.7)	62
	CK20	8/12 (66.7)	3/36 (8.3)	1/8 (12.5)	0/6 (0.0)	62

high MUC1 expression as a factor significantly linked to poor outcome assessed both by median survival and disease-free survival.

Gordon-Weeks, Alex N. MBChB, BSc, MRCS, DPhil; Jones, Keaton MRCS; Harriss, Elinor MSc, MA; Smith, Adrian MBBS, DPhil; Silva, Michael MBBS, MD, MS, FRCS (Gen), FRCS Ed. Systematic Review and Meta-analysis of Current Experience in Treating IPNB: Clinical and Pathological Correlates. Annals of Surgery 263(4):p 656-663, April 2016.

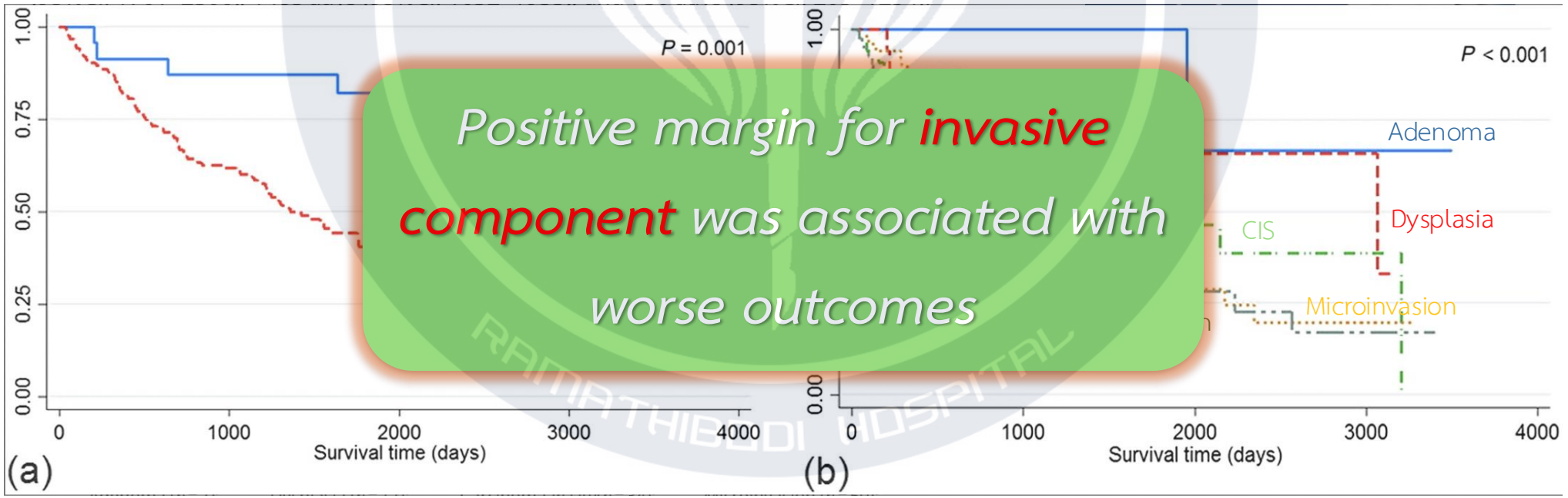
Journal of Gastroenterology and Hepatology
JGH JGHF

Biliary and Pancreatic | Full Access

Long-term outcome of surgical resection for intraductal papillary neoplasm of the bile duct

Vor Luvira, Ake Pugkhem, Vajarabhongsa Bhudhisawasdi, Chawalit Pairojkul, Egapong Sathitkarnmanee, Varisara Luvira, Supot Kamsa-ard

148 IPNB patients who underwent curative-intent hepatic resection between January 2005 and December 2011



*Positive margin for **invasive component** was associated with worse outcomes*

Retrospective Cohort Study

INTERNATIONAL JOURNAL OF SURGERY

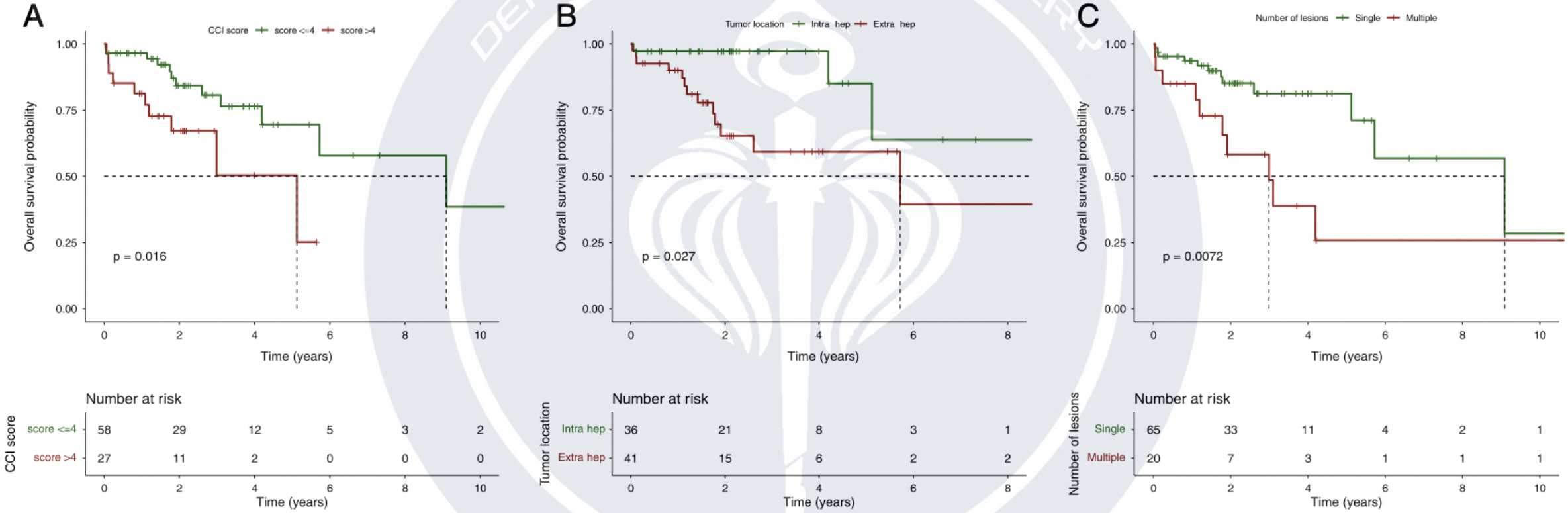
OPEN

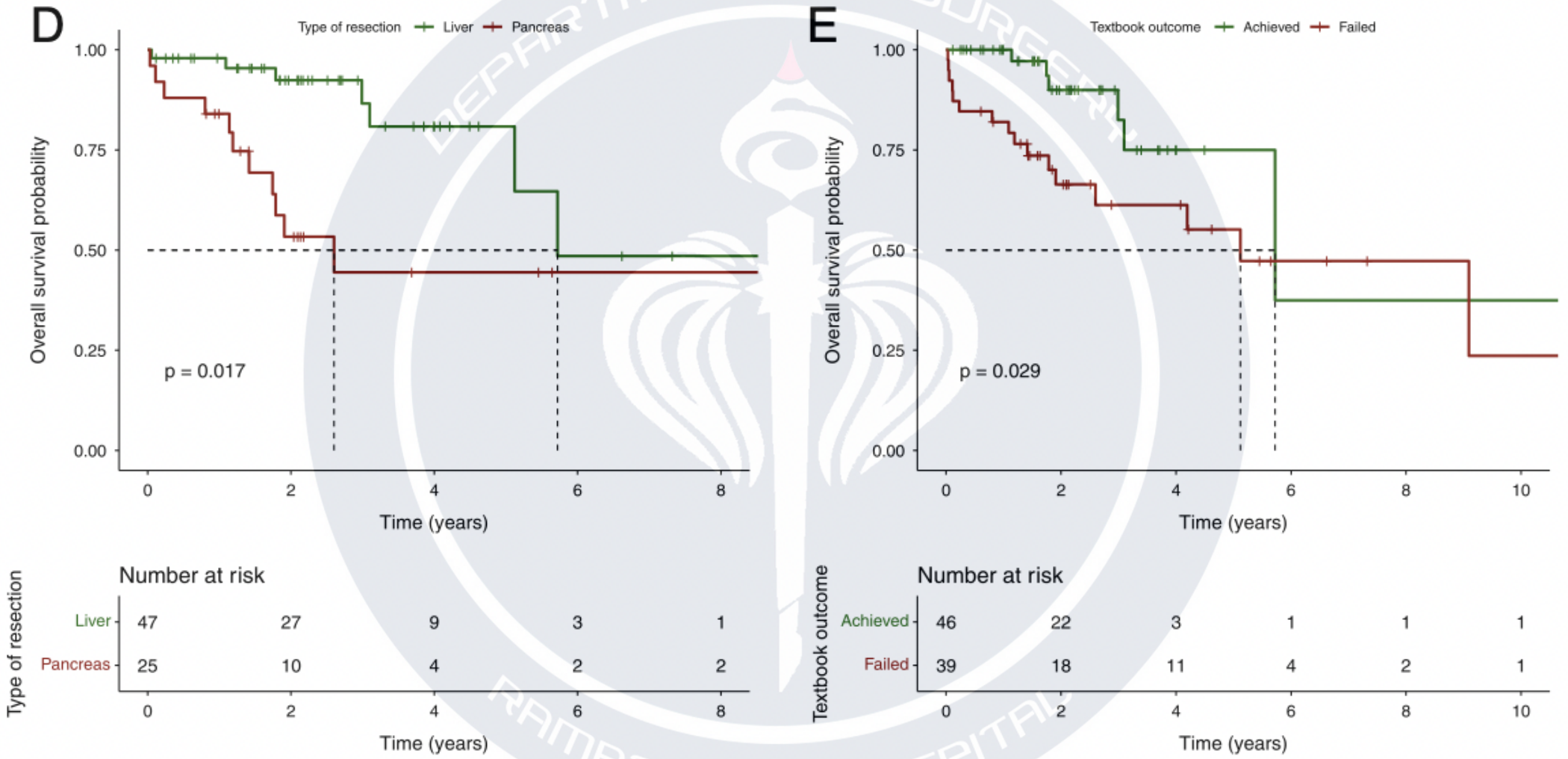
Intraductal papillary neoplasms of the bile duct: a European retrospective multicenter observational study (EUR-IPNB study)

Núria Lluís, MD[a], Mario Serradilla-Martín, MD, PhD, MSc[b,*], Mar Achalandabaso, MD, PhD[c], François Jehaes, MD[p], Bobby V.M. Dasari, MSc, MS, FRCS[x], Sara Mambrilla-Herrero, MD, PhD[f], Ernesto Sparrelid, MD, PhD[q], Anita Balakrishnan, BMBS, PhD, FRCS[v,w], Frederik J.H. Hoogwater, MD, PhD[n], Maria J. Amaral, MD[k,l], Bodil Andersson, MD, PhD[r,s], Frederik Berrevoet, MD, PhD[y], Alexandre Doussot, MD, PhD[o], Víctor López-López, MD, PhD[e], Mohammedsuror Alsammani, MD[cc], Olivier Detry, MD, PhD[z], Carlos Domingo-del Pozo, MD, PhD[g], Nikolaos Machairas, MD, PhD[dd], Damján Pekli, MD[u], Cándido F. Alcázar-López, MD, PhD[h], Horacio Asbun, MD, FACS[a], Bergthor Björnsson, MD, PhD[t], Thalis Christophides, MD, PhD, ChM(Ed)[hh], Alberto Díez-Caballero, MD, PhD[d], David Francart, MD[aa], Colin B. Noel, SA, FCS(SA), MBChB, MMed, BSc, ESB, BA[bb], Donzília Sousa-Silva, MD, MSc, FACS[m], Enrique Toledo-
François Cauch
Marius C. van d
José M. Ramia,
of the E-AHPBA

28 center, 85 patients

Retrospective study, Jan 2010 – Dec 2020


A
CCI score
score <=4
score >4
Overall survival probability
1.00
0.75
0.50
0.25
0.00
p = 0.016
0
2
4
6
8
10
Time (years)
Number at risk
CCI score
score <=4
58
29
12
5
3
2
score >4
27
11
2
0
0
0
Time (years)
B
Tumor location
Intra hep
Extra hep
Overall survival probability
p = 0.027
Time (years)
Number at risk
Tumor location
Intra hep
36
21
8
3
1
Extra hep
41
15
6
2
2
Time (years)
C
Number of lesions
Single
Multiple
Overall survival probability
p = 0.0072
Time (years)
Number at risk
Number of lesions
Single
65
33
11
4
2
1
Multiple
20
7
3
1
1
1
Time (years)


D
Type of resection
Liver
Pancreas
Overall survival probability
1.00
0.75
0.50
0.25
0.00
p = 0.017
0
2
4
6
8
Time (years)
Number at risk
Type of resection
Liver
47
27
9
3
1
Pancreas
25
10
4
2
2
0
2
4
6
8
Time (years)
E
Textbook outcome
Achieved
Failed
Overall survival probability
1.00
0.75
0.50
0.25
0.00
p = 0.029
0
2
4
6
8
10
Time (years)
Number at risk
Textbook outcome
Achieved
46
22
3
1
1
1
Failed
39
18
11
4
2
1
0
2
4
6
8
10
Time (years)

Non curative management

- Symptomatic treatment
- Biliary drainage
  - Preoperative planning : Endoscopic, EUS, PTBD
  - During exploration : biliary bypass(options) : bilioenteric anastomosis, Hepp-Couinaud approach(segment IV), Soupault – Couinaud approach (segment II/III)[1]
- ERCP guided RFA(ERFA)
  - Maintenance of biliary patency in 80% patients at 3 months[2]
  - Adverse event 17%(Hemobilia, partial liver infarction)
- Photodynamic therapy(PDT)[3]
- Palliative Chemotherapy
  - Insufficient data

[1]Myburgh JA. Resection and bypass for malignant obstruction of the bile duct. World J Surg. 1995;19(1):108–12.

[2]Laleman W, van der Merwe S, Verbeke L, et al. A new intraductal radiofrequency ablation device for inoperable biliopancreatic tumors complicated by obstructive jaundice: the IGNITE-1 study. Endoscopy. 2017;49:977–82.

[3]Zoepf T, Jakobs R, Arnold JC, Apel D, Riemann JF. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. Am J Gastroenterol 2005;100:2426–2430

Post operative outcomes

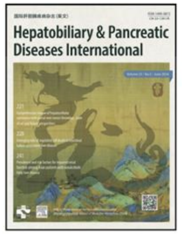
- 5-years Overall survival 47 – 80.8%
- Unfavorable Prognostic factors
  - R1 resection
  - Extrahepatic location
  - High MUC1, pancreaticobiliary type
  - Invasive disease
  - Nodal positive
  - Multiple lesion

Retrospective study

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

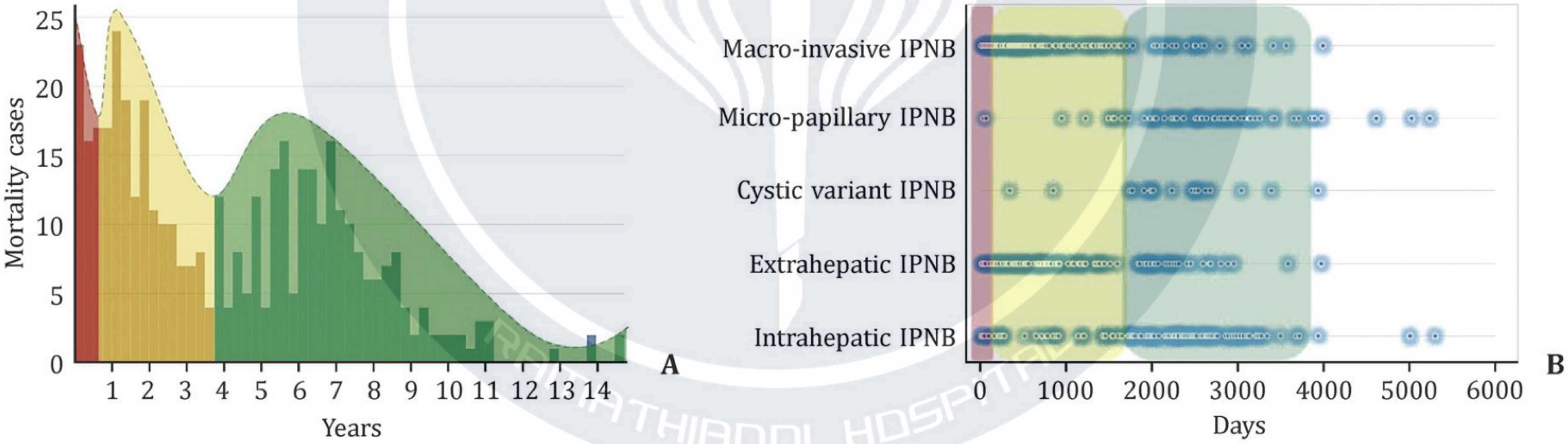


Viewpoint

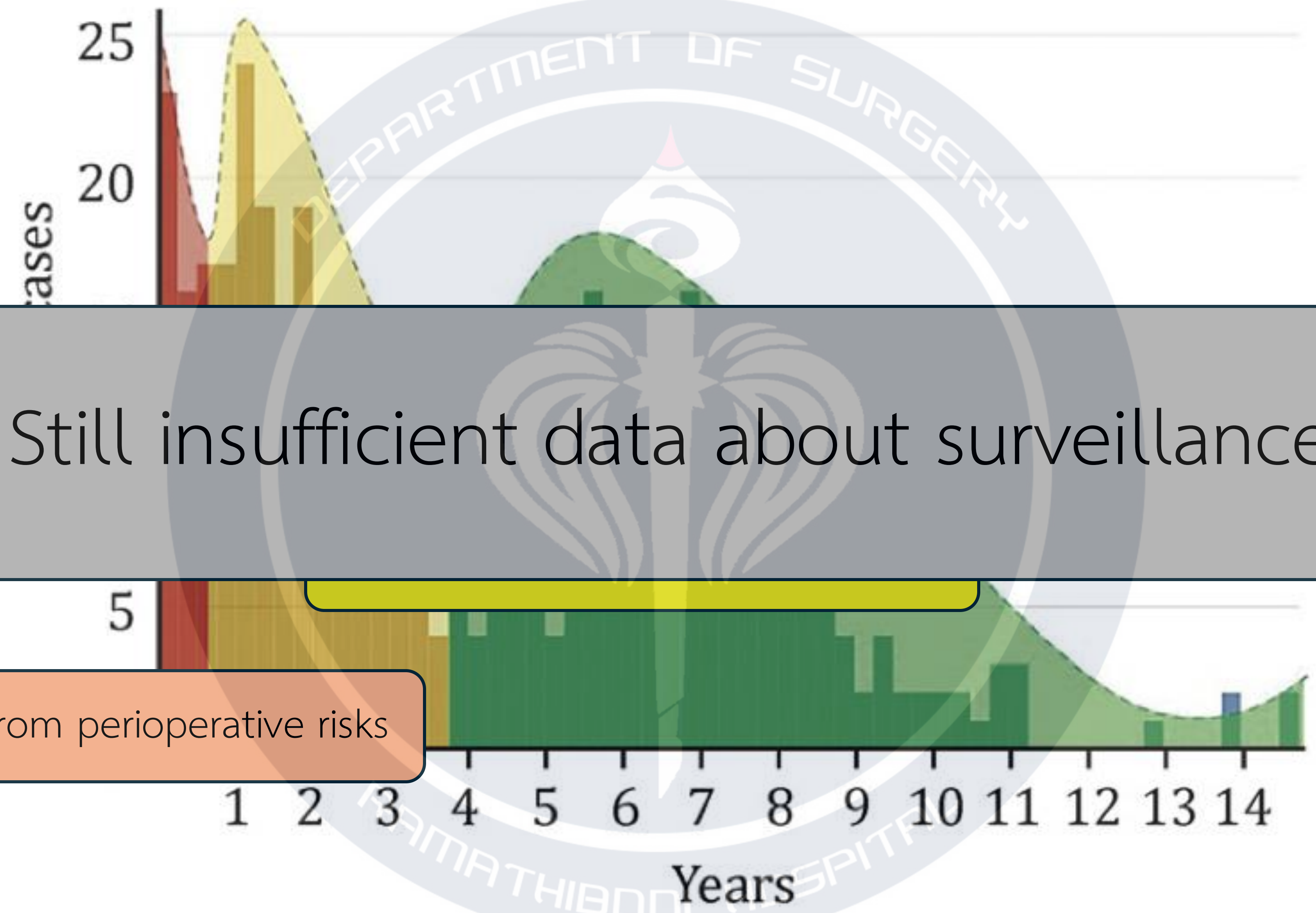
Tri-modal death distribution towards personalized management of intraductal papillary neoplasm of the bile duct patients: Every story has its own conclusion

Vor Luvira

Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand



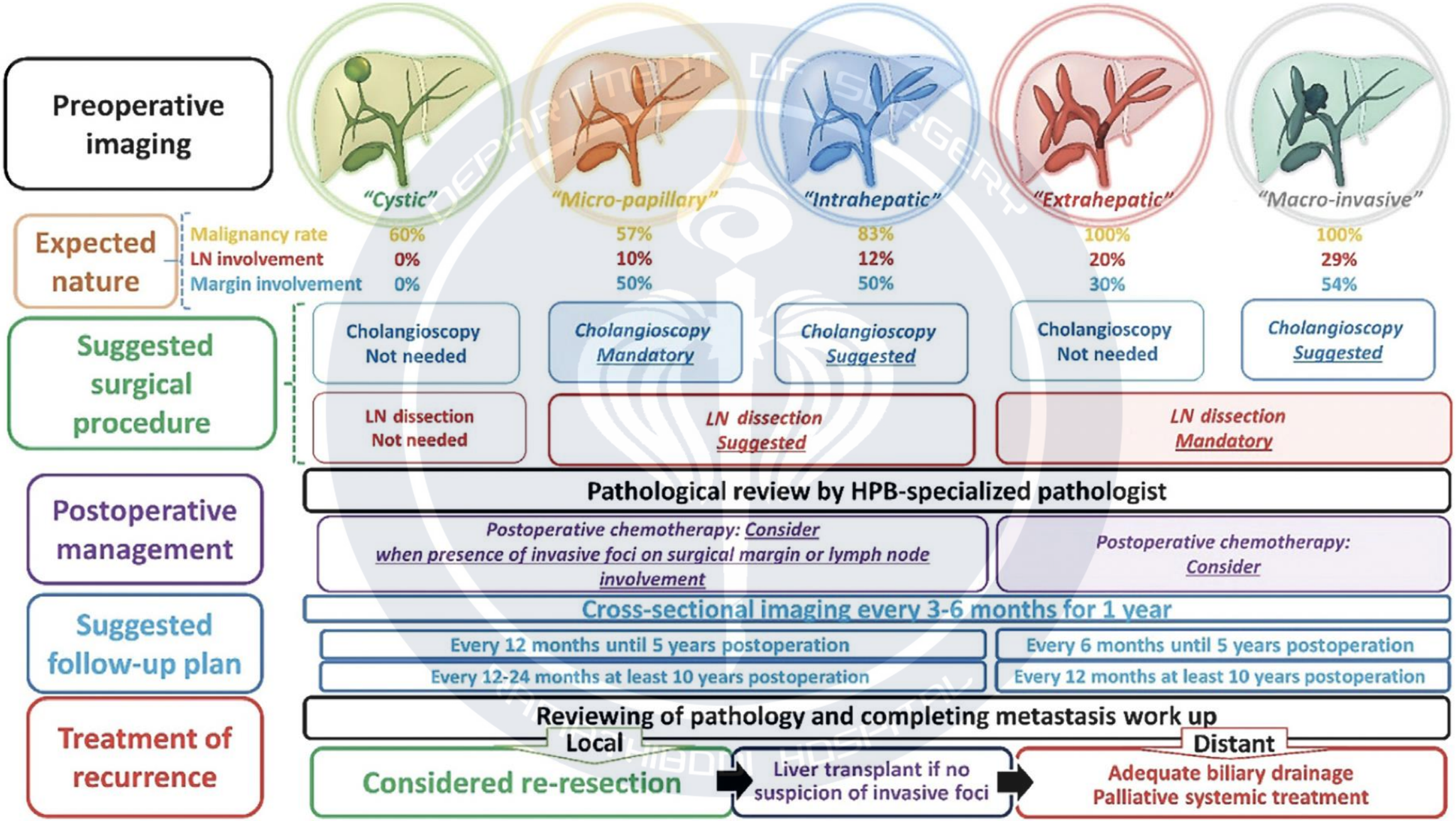
Luvira V. Tri-modal death distribution towards personalized management of intraductal papillary neoplasm of the bile duct patients: Every story has its own conclusion. Hepatobiliary Pancreat Dis Int. 2024 Jun;23(3):313-316. doi: 10.1016/j.hbpd.2024.01.004. Epub 2024 Jan 27. PMID: 38290936.



Still insufficient data about surveillance

Death from perioperative risks

Luvira V. Tri-modal death distribution towards personalized management of intraductal papillary neoplasm of the bile duct patients: Every story has its own conclusion. Hepatobiliary Pancreat Dis Int. 2024 Jun;23(3):313-316. doi: 10.1016/j.hbpd.2024.01.004. Epub 202… PMID: 38290936.


Preoperative imaging
"Cystic"
"Micro-papillary"
"Intrahepatic"
"Extrahepatic"
"Macro-invasive"
Expected nature
Malignancy rate 60% 57% 83% 100% 100%
LN involvement 0% 10% 12% 20% 29%
Margin involvement 0% 50% 50% 30% 54%
Suggested surgical procedure
Cholangioscopy Not needed
Cholangioscopy Mandatory
Cholangioscopy Suggested
Cholangioscopy Not needed
Cholangioscopy Suggested
LN dissection Not needed
LN dissection Suggested
LN dissection Mandatory
Postoperative management
Pathological review by HPB-specialized pathologist
Postoperative chemotherapy: Consider when presence of invasive foci on surgical margin or lymph node involvement
Postoperative chemotherapy: Consider
Suggested follow-up plan
Cross-sectional imaging every 3-6 months for 1 year
Every 12 months until 5 years postoperation
Every 6 months until 5 years postoperation
Every 12-24 months at least 10 years postoperation
Every 12 months at least 10 years postoperation
Treatment of recurrence
Reviewing of pathology and completing metastasis work up
Local
Distant
Considered re-resection
Liver transplant if no suspicion of invasive foci
Adequate biliary drainage
Palliative systemic treatment

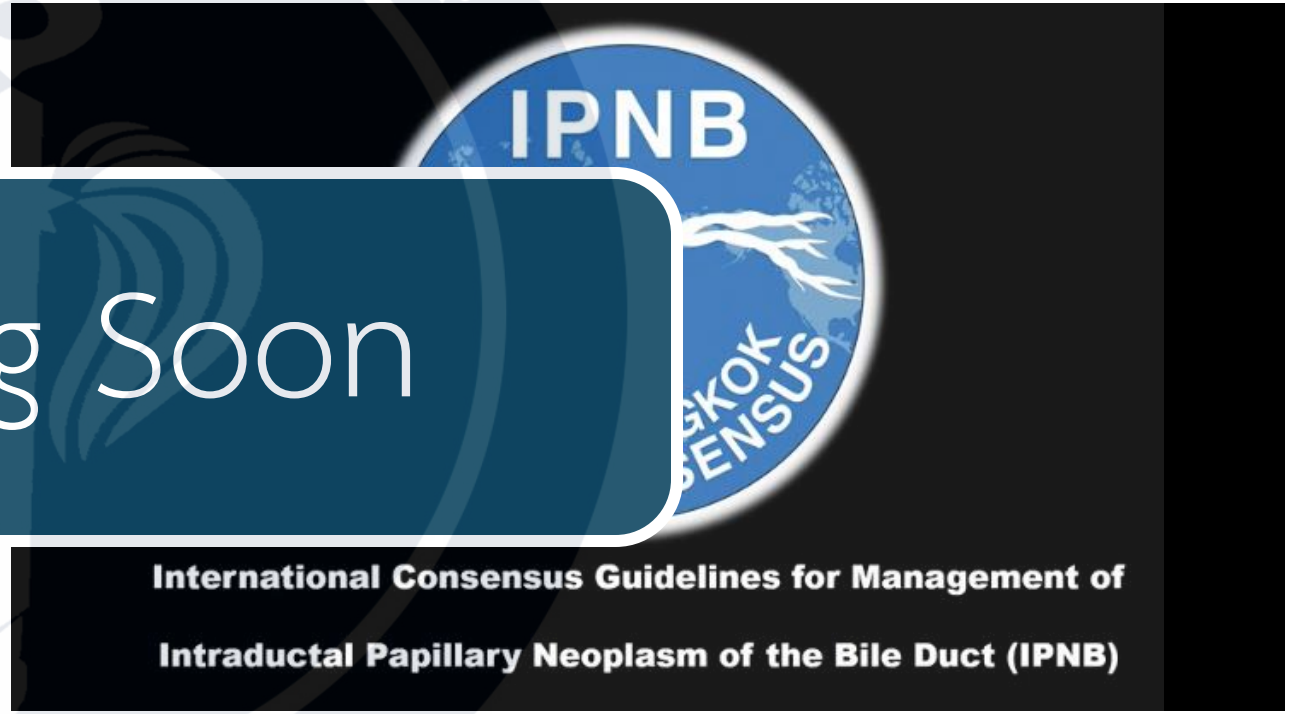
Take home message

- IPNB
  - Dilated intrahepatic and extrahepatic bile ducts filled with papillary or villous biliary neoplasm that covers delicate fibrovascular stalks
  - premalignant lesion towards invasive cholangiocarcinoma
- Risk factor
  - Asian : Hepatolithiasis and liver fluke infection
  - Western : primary sclerosing cholangitis (PSC) and congenital biliary tract disease
- Diagnostic
  - Various modality

Take home message

- **Subtype/Classification**
  - 4 subtype
  - Tumor grade
  - Japan-Korea
  - VL Classification
- **Management**
  - R0 resection is only curative intent
  - Margin : Invasive(Thai), High grade dysplasia(Korea) should be resected
  - Lymphadenectomy : routine lymphadenectomy

International consensus guidelines for management of IPNB



Coming Soon

Thank you