Intraductal papillary neoplasm of the bile duct: an European retrospective study (EUR-IPNB STUDY)

Serradilla-Martín M, Achalandabaso-Boira M, Lluis N <<participating surgeons>>, Charco R, Lesurtel M, Ramia-Ángel JM, on behalf of the European-African Hepato-Pancreato-Biliary Association

Study coordinators:

Mario Serradilla Martín
Senior Consultant HPB Surgeon
Department of Surgery
Miguel Servet University Hospital
Zaragoza, Spain
Tel: + 34 636006184
e-mail: marioserradilla@hotmail.com

Mar Achalandabaso Boira
Consultant HPB Surgeon
Department of HPB Surgery and Liver Transplantation
Hospital Universitari Vall d'Hebron
Barcelona, Spain
Tel: +93 4893000
e-mail: m.achalandabasoboira@gamil.com

Nuria Lluis (data manager coordinator)
Nuria Lluis
Research Fellow, Surgical Oncology
Division of Hepatobiliary and Pancreas Surgery, Miami Cancer Institute, Miami, Florida, USA.
Telf: +1 786 596 2000
E-mail: nuria.lluisvinas@baptisthealth.net

Main investigators:

José Manuel Ramia Ángel
Head of Department
Department of Surgery and Liver Transplantation
Alicante General University Hospital
Alicante, Spain
Tel.: + 34 616292056
e-mail: jose_ramia@hotmail.com

Mickaël Lesurtel
Department of Digestive Surgery and Liver Transplantation
Croix Rousse University Hospital
Lyon, France
Tel: +33472071100
e-mail: mickael.lesurtel@chu-lyon.fr

Ramón Charco
Head of Deparment
Department of HPB Surgery and Liver Transplantation
Hospital Universitari Vall d'Hebron
Barcelona, Spain
Tel: +93 4893000
e-mail: rcharco@gmail.com

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LIST OF ABBREVIATIONS

CRF: Case report form

E-AHPBA: European-African Hepato-Pancreato-Biliary-Association

IPNB: Intraductal papillary neoplasm of the bile duct

IPMN: Intraductal pancreatic mucinous neoplasm

1. PROTOCOL ABSTRACT

Background. Intraductal papillary neoplasm of the bile duct (IPNB) is a rare and relatively unknown entity, considered as the biliary equivalent of intraductal papillary mucinous neoplasm (IPMN) of the pancreas. Since 1960 there have been increasing reports of a variety of mucin-secreting papillary and cystic lesions of the intra and extrahepatic bile tract. In 2001, Chen and Nakanuma proposed the IPNB concept. Finally, in 2010, IPNB was included in the classification of the World Health Organization as a distinct clinical pathological entity. Several names have been previously used previously: "intraductal papillary tumor of the bile duct", “biliary intraductal papillary neoplasm”, “biliary papillomatosis” and “invasive biliary mucinous cystic neoplasm”. Most of the information about IPNB comes from Asia and very few information about European patients with IPNB is published.

Aim. To assess the real prevalence and incidence, indications, perioperative and postoperative outcomes, and survival of IPNB patients across E-AHPBA centres.

Methods. A retrospective multicenter cohort study will include all consecutive patients who underwent liver or biliary surgery for IPNB between January 1st 2010 and June 30th 2020. Predefined electronic case report forms will be disseminated among participating centres. Participants are responsible for their own data collection. Primary outcome will survival at 1-3-5 years. Secondary objectives will be 90-day outcomes.

Strengths. This multicenter study will involve a large number of European centres, so it will allow to collect data about a rare disease across Europe.

Limitations. The most important limitation is the discrepancy in surgical indication between each centre. The accuracy of the measurement of outcomes is limited by inter-center heterogeneity in data collection and reporting, surgical case selection, variability of surgical procedure, and postoperative management.

PLANNING. The data collection will start on September 1st 2021 and will last for 3 months. Data-analysis and manuscript completion are expected around January 2022.

2. INTRODUCTION

Intraductal papillary neoplasm of the bile duct (IPNB) is a rare and little known entity, considered as the biliary equivalent of intraductal papillary mucinous neoplasm of the pancreas (IPMN). Since 1960 there have been increasing reports of a variety of mucin-secreting papillary and cystic lesions of the intra and extrahepatic biliary tract. In 2001, the concept of IPNB was proposed by Chen and Nakanuma, who noted that intraductal papillary neoplasms of the bile duct, with goblet cells and colon-like metaplasia were associated with an overproduction of mucin and mucobilia. Finally, in 2010, IPNB was included in the classification of the World Health Organization as a distinct clinical pathological entity defined as grossly visible premalignant lesions of the liver and bile ducts with intraductal papillary or villous growth of biliary-type epithelium. In the last edition they were divided into low-grade, high-grade and IPNB with associated invasive adenocarcinoma.

IPNB is considered a premalignant condition, with an increasing number of cases identified and reported. It seems to be gaining popularity possibly due to an improvement in imaging techniques but also a better anatomopathological description. It can be seen as a filling defect in the biliary tree but may be undetectable radiologically and only diagnosed incidentally after surgical resection.

The prevalent location is highly variable among studies and the median patient age is 50-70 with a male predominance. Mostly found in East Asia, although present worldwide, still seems to be underdiagnosed. The etiology is unclear but known risk factors are liver fluke infection, primary sclerosing cholangitis and hepatolithiasis. IPNB follow a sequential progression added to the mutations of common oncogenic pathways. Literature is lacking regarding standardised diagnosis and treatment protocols.

Given its potential for malignization into cholangiocarcinoma, taking into account that at the time of surgery a significant proportion have already stromal invasion associated with invasive carcinoma, early diagnosis and treatment seem of paramount importance. Studies regarding IPNB are limited to small patient numbers and suggest early and aggressive surgery as the best approach. The study proposed here is a large, international, multicenter study, which will overcome the bias related to small patient numbers and finally allow some clear recommendations to be made to optimise the time and the type of interventions. We aim to establish the real incidence of this relatively new entity in European countries and standardize its current management.

3. METHODS

This is a European retrospective series within participating centres represented by members of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA).

3.1 Patients and design

All consecutive patients who underwent an elective liver or biliary surgery for IPNB between January 1st 2010 and June 31th 2020 will be collected.

Retrospective international multicentre analysis to assess the aims above and allow identification of key avenues for further studies. In keeping with current ongoing similar database studies, patients will not undergo an individual consent process for recruitment of this study, as no intervention will be performed or any change to existing treatment protocols, and only de-identified data will be made available to non-clinical teams. In addition, as this is an international multicentre study with collaborators anticipated from many countries, mandating consent from each patient recruited is likely to reduce recruitment due to the need for translation of consent forms into specific native languages, as well as the resource limitations in each country and unit that may often lack research teams available to obtain consent.

3.2 Inclusion criteria

Inclusion criteria

All patients operated on with IPNB between January 2010 and June 2020.

Exclusion criteria

Patients without confirmed pathological IPNB diagnosis.

Patients who did not undergo surgery.

3.3 Definitions

Patients' comorbidities are summarized according to Charlson Comorbidity Index. Intraoperative complications are categorized according to Satava's classification. Postoperative complications are scored and classified using the Clavien-Dindo classification of surgical complications. Major complications are defined as Clavien-Dindo grade IIIa or higher. Resection margins, including transection and circumferential margins, are categorized according to the Royal College of Pathologists definition and classified into R0 (distance margin to tumor ≥ 1mm), R1 (distance margin to tumor < 1mm) and R2 (macroscopically positive margin). Complications, re-admissions and mortality are all recorded up to 90-days postoperatively. Posthepatectomy haemorrhage, biliary leakage and liver failure, are categorized according to the definitions of the International Study Group of Liver Surgery (ISGLS). Pancreatic fistula and delayed gastric empting are categorized according to the definitions of the International Study Group of Pancreas Surgery (ISGPS).

3.4 Objectives

Primary objectives

Assess the incidence, prevalence and current management of IPNB in order to gain better understanding and provide clinical recommendations.

Secondary objectives

Identify prognostic/risk factors predicting worse overall survival and disease-free survival.

Standardise pathological reporting.

3.5 Data collection

Each participating center will appoint one dedicated contact person, responsible for all communication with the study coordinator. Each center will subsequently receive a link to an on-line survey. This survey will inquire information about current implementation of IPNB, annual case volumes, and standards of care at the participant institution. This information may be used in the analyses, as a base for subgroup or sensitivity analyses.

Each center will subsequently receive a login codes and passwords for the on-line electronic case report form (eCRF) environment (REDCap®, Research Electronic Data Capture). Each data collector will receive a separate login account of which all activity can be monitored by the chief study coordinators. All edit and audit trails will be logged in conformity with Good Clinical Practice (GCP) guidelines. All variables collected are listed in Appendix 1.

3.6 Ethics

Approval from Ethics Committee of Alicante General Hospital will be obtained. All data will be collected anonymously, without patient identifiers. Participating centers will be asked to link the patient's local medical record numbers to an anonymous study patient ID. This information will be stored locally at the responsibility of participating centers. In case additional data extraction is needed, participating centers may be asked to re-identify the patient based on the study patient ID.

All amendments to the protocol will be discussed with the Ethics Committee of Alicante General Hospital. Advice will be taken on the regulatory approvals required for the amendments. Amendments submitted for regulatory review will not be implemented until the necessary regulatory approvals are received.

3.7 Statistical analysis

Data will be analyzed using R (R-2.14.1 2011 software (The R Foundation for Statistical Computing). Student's t, Mann Whitney U, Chi-square, or Fisher's exact tests will be used as appropriate. Categorical data will be expressed as frequency and percentage. Continuous data will be expressed either as mean and standard deviation or as median and interquartile range depending on the distribution of the data. Subgroups will be performed to compare characteristics and treatment outcomes, using Chi-square test, Mann-Whitney U test and Kruskal Walls test as appropriate. Alpha < 0.05 will be used to indicate statistical significance.

Long Term Data Storage

De-identified data will be stored on a secure password-protected database and for 10 years after study findings are published in order to ensure that findings are verifiable. We propose the duration of 10 years as this is very valuable data from an international collaboration of multiple centers, and we anticipate that elements of the data collected could be analysed again in the future for validation of any newer findings that emerge in the literature, to maximise the use of this precious resource and avoid duplication of effort to collect such data again.

4. AUTHORSHIP AND PUBLICATION POLICY

Authorships will be based on the International Committee of Medical Journal Editors (ICMJE) guideline (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

Centres providing at least one case will be eligible for 1 authorship position, with eligibility for 2 authorship positions when providing at least 4 IPNB cases.

Each participating centre will decide internally which local investigator will be listed as co-author. The first authorship position is reserved for the study coordinator (MSM, MAB). Principal investigators (RC, ML and JMRA) will be listed as senior authors in the last position. All other authors will be listed according to the number of patients included. Any publication, presentation or abstract on collected data will be delegated to all authors. Each centre remains the possessor of their own data and additional reports on data collected will only be conducted in case of written author permission.

5. REFERENCES

1. Hong MY, Yu DW, Hong SG. Intraductal papillary mucinous neo- plasm of the bile duct with gastric and duodenal fistulas. World J Gastrointest Endosc 2014; 6: 328-33
2. Barton JG, Barrett DA, Maricevich MA, Schnelldorfer T, Wood CM, Smyrk TC et al. Intraductal papillary mucinous neoplasm of the biliary tract: a real disease? HPB 2009; 11: 684-91.
3. WHO Classification of Tumours of Digestive System. 5th ed. WIARC: Lyon, France. 2019. 250–253 p.
4. Kubota K, Jang JY, Nakanuma Y, Jang KT, Haruyama Y, Fukushima N, et al. Clinicopathological characteristics of intraductal papillary neoplasm of the bile duct: a Japan-Korea collaborative study. J Hepatobiliary Pancreat Sci. 2020 Sep 1;27(9):581–97.
5. Zen Y, Sasaki M, Fujii T, Chen TC, Chen MF, Yeh T Sen, et al. Different expression patterns of mucin core proteins and cytokeratins during intrahepatic cholangiocarcinogenesis from biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct - An immunohistochemical study of 110 cases of hepatolithiasis. J Hepatol. 2006 Feb 1;44(2):350–8.
6. Yang CY, Huang WJ, Tsai JH, Cheng A, Chen CC, Hsu HP, et al. Targeted next-generation sequencing identifies distinct clinicopathologic and molecular entities of intraductal papillary neoplasms of the bile duct. Mod Pathol. 2019 Nov 1;32(11):1637–45.
7. Nakanuma Y, Uesaka K, Kakuda Y, Sugino T, Kubota K, Furukawa T, et al. Intraductal Papillary Neoplasm of Bile Duct: Updated Clinicopathological Characteristics and Molecular and Genetic Alterations. J Clin Med. 2020 Dec 9;9(12):3991.
8. Kubota K, Nakanuma Y, Kondo F, Hachiya H, Miyazaki M, Nagino M, et al. Clinicopathological features and prognosis of mucin- producing bile duct tumor and mucinous cystic tumor of the liver: a multi-institutional study by the Japan Biliary Association. J Hepatobiliary Pancreat Sci 2014; 21: 176-85.
9. 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: 459091.
10. Rocha FG, Lee H, Katabi N, DeMatteo RP, Fong Y, D'Angelica MI et al. Intraductal papillary neoplasm of the bile duct: a biliary equivalent to intraductal papillary mucinous neoplasm of the pancreas? Hepatology 2012; 56: 1352-60.
11. Ohtsuka M, Kimura F, Shimizu H, Yoshidome H, Kato A, Yoshitomi H et al. Surgical strategy for mucin-producing bile duct tumor. J Hepatobiliary Pancreat Sci 2010; 17: 236-40.
12. Kim KM, Lee JK, Shin JU, Lee KH, Sung JY, Jang KT et al. Clinicopathologic features of intraductal papillary neoplasm of the bile duct according to histologic subtype. Am J Gastroenterol 2012; 107: 118-25.
13. Kawaguchi Y, Kawashima Y, Maruno A, Ito H, Ogawa M, Izumi H et al. An intraductal papillary neoplasm of the bile duct at the duodenal papilla. Case Rep Oncol 2014; 7: 417-21.
14. Chen TC, Nakanuma Y, Zen Y, Chen MF, Jan YY, Yeh TS et al. Intraductal papillary neoplasia of the liver associated with hepato-lithiasis. Hepatology 2001; 34: 651-8.
15. Kim BS, Joo SH, Lim SJ, Joo KR. Intrahepatic biliary intraductal papillary mucinous neoplasm with gallbladder agenesis: case report. Surg Laparosc Endosc Percutan Tech 2013; 23: e61-e64.
16. Sessa F, Solcia E, Capella C, Bonato M, Scarpa A, Zamboni G et al. Intraductal Papillary-Mucinous Tumours Represent a Distinct Group of Pancreatic Neoplasms: An Investigation of Tumour Cell Differentiation and K-Ras, p53 and c-erbB-2 Abnormalities in 26 Patients.Virchows Archiv 1994; 425: 357-67.
17. Adsay V, Mino-Kenudson M, Furukawa T, Basturk O, Zamboni G, Marchegiani G et al. Pathologic evaluation and reporting of in traductal papillary mucinous neoplasms of the pancreas and

other tumoral intraepithelial neoplasms of pancreatobiliary tract. Ann Surg 2015:1-16.
18. Zen Y, Fuji T, Itatsu K, Nakamura K, Minato H, Kasashima S et al. Biliary papillary tumors share pathological features with intra- ductal papillary mucinous neoplasm of the pancreas. Hepatology 2006; 44: 1333-43.
19. Ji Y, Fan J, Zhou J, Wang BS, Liu HB, Wu ZW et al. Intraductal papillary neoplasms of bile duct. A distinct entity like its counter- part in pancreas. Histology and Histopathology 2008; 23: 41-50.
20. Nakanuma Y, Sasaki M, Ishikawa A, Tsui W, Chen TC, Huang SF. Biliary Papillary Neoplasm of the Liver. Histology and Histopa- thology 2002; 17: 851-61.
21. Yamashita Y, Fukuzawa K, Taketomi A, Aishima S, Yoshizumi T, Uchiyama H et al. Mucin-Hypersecreting Bile Duct Neoplasm Characterized by Clinicopathological Resemblance to Intraductal Papillary Mucinous Neoplasm (IPMN) of the Pancreas. World journal of surgical oncology 2007; 5: 98.
22. Furukawa T, Klöppel G, Volkan Adsay N, Albores-Saavedra J, Fukushima N, Horii A et al. Classification of Types of Intraductal Papillary-Mucinous Neoplasm of the Pancreas: A Consensus Study. Virchows Archiv 2005; 447: 794-99.
23. Sclabas GM, Barton JG, Smyrk TC, Barrett DA, Khan S, Kendrick ML et al. Frequency of subtypes of Biliry Intraductal Papillary Mucinous Neoplasm and their MUC1, MUC2 and DPC4 expression patterns differ from Pancreatic Intraductal Papillary Mucinous Neoplasm. Journal of the American College of Sur- geons 2012; 214: 27-32.
24. Ohtsuka M, Kimura F, Shimizu H, Yoshidome H, Kato A, Yoshitomi H et al. Similarities and differences between intraductal papillary tumors fo the bile duct with and without macroscopically visible mucin secretion. Am J Surg Pathol 2011; 35: 512-21.
25. Lim JH, Yoon KH, Kim SH, Kim HY, Lim HK, Song SY et al. Intraductal papillary mucinous tumor of the bile ducts. Radiograph- ics 2004; 24: 53-66.
26. Choi SC, Lee JK, Jung JH, Lee JS, Lee KH, Lee KT et al. The clinicopathological features of biliary intraductal papillary neoplasms according to the location of tumors. J Gastroenterol Hepa-tol 2010; 25: 725-30.
27. Yun S, Choi D. Ruptured intrahepatic bliary intraductal papillary mucinous neoplasm in a Jehovah's Witness patient. Int Surg 2014;99: 590-94.
28. Takanami K, Yamada T, Tsuda M, Takase K, Ishida K, Nakamura Y et al. Abdom imaging 2011; 36: 447-56.
29. Ogawa H, Itoh S, Nagasaka T, Suzuki K, Ota T, Naganawa S. CT findings of intraductal papillary neoplasm of the bile duct: assess- ment with multiphase contrast-enhanced examination using multi-detector CT. Clin Radiol 2012; 67: 224-31.
30. Yoon HJ, Kim YK, Jang KT, Lee KT, LeeJK Choi DW et al. Intraductal papillary neoplasm of the bile ducts: description of MRI and added value of diffusion-weighted MRI. Abdom Imaging 2013; 38: 1082-90.
31. Yeh TS, Tseng JH, Chiu CT, Liu NJ, Chen TC, Jan YY et al. Cholangiographic spectrum of intraductal papillary mucinous neo-plasm of the bile ducts. Ann Surg 2006; 244: 248-53.
32. Tsuyuguchi T, Sakai Y, Sugiyama H, Miyakawa K, Ishihara T, Ohtsuka M et al. Endoscopic diagnosis of intraductal papillary mucinous neoplasm of the bile duct. J Hepatobiliary Pancreat Sci2010; 17: 230-35.
33. Sakai Y, Tsuyuguchi T, Tsuchiya S, Fukuda Y, Miyakawa K, Sugi- yama H et al. Value of peroral cholangioscopy for mucin-producing bile duct tumor. Hepatogastroenterology 2008;55(81):58-61.
34. Neuhaus H. Peroral and percutaneous transhepatic cholangioscopy. Bildgebung 1993; 60: 190-4.
35. Sakai Y, Tsuyuguchi T, Tsuchiya S, Fukuda Y, Miyakawa K, Sugi-yama H et al. Clinical utility of

peroral cholangioscopy for mucin- producing bile duct tumor. Hepatogastroeneterolgy 2008; 55: 1509-12.
36. Tamada K, Nagai H, Yasuda Y, Tomiyama T, Ohashi A, Wada S et al. Transpapillary intraductal US prior to biliary drainage in the assessment of longitudinal spread of extrahepatic bile duct carci- noma. Gastrointest Endosc 2001; 53: 300-7.
37. Sohn WJ, Jo S. A Huge Intraductal Papillary Mucinous Carcinoma of the Bile Duct Treated by Right Trisectionectomy with Caudate Lobectomy. World journal of surgical oncology 2009; 7: 93.
38. Yaman B, Nart D, Yilmaz F, Coker A, Zeytunlu M, Kilic M. Bili-ary Intraductal Papillary Mucinous Neoplasia: Three Case Re- ports. Virchows Archiv 2009; 454: 589-94.
39. Minagawa N, Sato N, Mori Y, Tamura T, Higure A, Yamaguchi K. A Comparison between Intraductal Papillary Neoplasms of the Biliary Tract (BT-IPMNs) and Intraductal Papillary Mucinous Neoplasms of the Pancreas (P-IPMNs) Reveals Distinct Clinical Manifestations and Outcomes. European Journal of Surgical Oncology 2013; 39: 554-58.
40. Hu LH, Liu MH, Liao Z, Zou WB, Ye B, Wang L et al. Continu- ous infusion of N-acetylcysteine by nasobiliary for advanced in- traductal papillary mucinous neoplasm of bile ducts (with video). Am J Gastroenterol 2012; 107: 1929-30.
41. Valente R, Capurso G, Pierantognetti P, Iannicelli E, Piciucchi M, Romiti A et al. Simultaneous intraductal papillary neoplasms of the bile duct and pancreas treated with chemoradiotherapy. World J Gastrointest Oncol 2012; 4: 22-25.
42. Ohtsubo I, Ajiki T, Hori Y, Murakami S, Shimizu K, Itoh T et al. Distinctive expression of CD133 between intraductal papillary neoplasms of the bile duct and bile duct adenocarcinomas. Hepa- tol Res 2012; 42: 574-82.
43. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205-13.
44. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastricemptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142(5):761-8.
45. Besselink MG, van Rijssen LB, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition and classification of chyle leak after pancreatic operation: A consensus statement by the International Study Group on Pancreatic Surgery. Surgery. 2017;161(2):365-72.
46. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142(1):20-5.
47. The Royal College of Pathologists. Standards and Minimum Datasets for Reporting Cancers Minimum dataset for the histopathological reporting of pancreatic, ampulla of Vater and bile duct carcinoma. London R Coll Pathol. 2002.
48. Roffman C, Buchanan J, Allison G.T. Charlson Comorbidities Index. J Physiother 2016; 62(3):171.
49. Satava RM. Identification and reduction of surgical error using simulation. Minim Invasive Ther Technol 2005; 14:257–261.
50. Rahbari N, Garden J, Padbury R, et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). HPB 2011; 13(8):528-35.
51. Brooke M, Figueras J, Ullah S, et al. Prospective evaluation of the International Study Group for Liver Surgery definition of bile leak after a liver resection and the role of routine operative drainage: an international multicentre study. HPB 2015;17(1):46-51.
52. Rahbari N, Garden J, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011. 149:713-724.

Appendix 1

Baseline and outcome variables

Table 1. Variables to identify

1. VARIABLE	**FORMAT**
1.1 Hospital	Drop-down
1.2 Case ID	Site name_res_no
2. BASELINE	
2.1 Gender	M/F
2.1.1 Ethnic	Asian/Caucasian/African/Latin/Other
2.2 Date of birth	DD/MM/YYYY
2.3 Operation date	DD/MM/YYYY
2.4 Patient age at operation time	Calculation
2.5 Height	cm
2.6 Preoperative weight	Kg
2.7 BMI	Calculation
2.8 ASA Score	(I/II/III/IV/V/Unknown)
2.9 ECOG performance status	(0/1/2/3/4)
2.10 Charlson Comorbidity Index (CCI)	Drop-Down
2.10.1 Prior myocardial infarction	N/Y
2.10.2 Congestive heart failure	N/Y
2.10.3 Peripheral vascular disease	N/Y
2.10.4 Cerebrovascular disease	N/Y
2.10.5 Dementia	N/Y
2.10.6 Chronic pulmonary disease	N/Y
2.10.7 Rheumatologic disease	N/Y
2.10.8 Peptic ulcer disease	N/Y
2.10.9 Mild liver disease	N/Y
2.10.10 Diabetes	N/Y
2.10.11 Cerebrovascular event	N/Y
2.10.12 Moderate- severe renal disease	N/Y
2.10.13 Diabetes with chronic complications	N/Y
2.10.14 Cancer without metastases	N/Y
2.10.15 Leukemia	N/Y
2.10.16 Lymphoma	N/Y
2.10.17 Moderate or severe liver disease	N/Y
2.10.18 Metastatic solid tumor	N/Y
2.10.19 Acquired immuno-deficiency syndrome (AIDS)	N/Y
2.10.20 Score	Sumatory 2.10.1 to 2.10.19
2.10.21 Estimated survival at 10 years (%)	Percent
2.11 Past surgical history	Y/N/Unknow
2.11.1 If yes, abdominal surgery	
2.12 Cirrhosis	Drop-Down
2.13 Child	
2.14 Past medical history-liver related	
3**. PREOPERATIVE DATA**	
3.1 CLINICAL DETAILS	
3.1.1 Abdominal pain	N/Y
3.1.2 Jaundice	N/Y
3.1.3 Asymptomatic	N/Y
3.1.4 Acute cholangitis	N/Y
3.1.5 Preoperative bilirubin (mg/dL)	
3.1.6 Preoperative CA 19.9 (U/ml)	

3.2 PREDISPOSALS FACTOR	
3.2.1. Hepatolithiasis	N/Y
3.2.2 Clonorchis Infestation	N/Y
4. DIAGNOSTIC METHODS	
4.1 Date of diagnosis	DD/MM/YYYY
4.4 Location	Pancreas/bile duct/Gallbladder/Liver
4.5 Diameter	mm
4.6 IPNB pre-operatory image diagnosis	
4.6.1 Computerized tomography (CT)	N/Y
Correct preoperative IPNB diagnosis	N/Y
4.6.2 Magnetic resonance (MR)	N/Y
Correct preoperative IPNB diagnosis	N/Y
4.6.3 Abdominal Ultrasound	N/Y
Correct preoperative IPNB diagnosis	N/Y
4.6.4 ERCP	N/Y
Correct preoperative IPNB diagnosis	N/Y
4.6.5 Ultrasound endoscopy USE	N/Y
Correct preoperative IPNB diagnosis	N/Y
4.6.6 Endoscopy cholangioscopy	N/Y
Correct preoperative IPNB diagnosis	N/Y
4.6.7 PTC	N/Y
Correct preoperative IPNB diagnosis	N/Y
4.7 Findings	Mass/ductal ectasia/ ductal stenosis/duct dilatation (Multiple choice)
4.8 Pancreas affected	N/Y
4.9 Location	Intrahepatic/Biliary EH/Biliary intrapancreatic(Multiple choice)
4.10 Tumor (number)	Unique/Multifocal
4.11 Size tumor (bigger)	
4.12 Preoprative biopsy compatible with IPNB	
4.13 IPNB was suggested as a possibility	
4.14 IPNB was highly likely to be the cause	cm
4.15 Prior test suggested the possibility of IPNB	
4.15.1 Which test: US/CT/MRI	
4.16 Preoperative drainage	
5. INTRA-OPERATIVE DETAILS	
5.1 Surgical approach	Laparoscopic / open / robotic
5.2 Intra-operative events (Satava classification)	
5.2.1 None	N/Y
5.2.2 Grade 1(excessive blood loss, damage to surrounding structures - not requiring conversion)	N/Y
5.2.3 Grade 2 (conversion or major change to planned operation)	N/Y
5.2.4 Grade 3 (intra-operative death)	N/Y
5.3 Intraoperative convertion surgery	N/Y
5.3.1 If yes, reason of convertion	
5.3.1.1 Bleeding	N/Y
5.3.1.2 Vascular involvement	N/Y
5.3.1.3 Adhesions	N/Y
5.3.1.4 Insufficient overview	N/Y
5.3.1.5 Technical reason	N/Y
5.3.1.6 Tumor advancement	N/Y
5.3.1.7 Other reason	Free text
5.4 Intraluminal mucin	

Combined surgeries performed

LIVER RESECTION	N/Y
5.5 Pringle maneuver	N/Y
5.5.1 If yes, time of vascular clamping	Minutes
5.6 Operation time	Minutes
5.7 Estimated blood loss	ml
5.8 Perioperative blood transfusion	N/Y
5.8.1 If yes, number of red blood cells concentrates	Number
5.9 Primary operation performed	
5.9.1 Atypical / Non-anatomical	N/Y
5.9.2 Left lateral sectionectomy (2 & 3)	N/Y
5.9.3 Bisegmentectomy (5 & 6)	N/Y
5.9.4 Right anterior sectionectomy (5 & 8)	N/Y
5.9.5 Right posterior sectionectomy (6 & 7)	N/Y
5.9.6 Left hemi-hepatectomy (2, 3 & 4)	N/Y
5.9.7 Right hemi-hepatecomy (5, 6, 7 & 8)	N/Y
5.9.8 Central hepatectomy (4, 5, & 8)	N/Y
5.9.9 Extended right hepatect. (4, 5, 6, 7 & 8)	N/Y
5.9.10 Extended left hepatect. (2, 3, 4, 5 & 8)	N/Y
5.9.11 Segment 1 wedge resection	N/Y
5.9.12 Segment 2 wedge resection	N/Y
5.9.13 Segment 3 wedge resection	N/Y
5.9.14 Segment 4 wedge resection	N/Y
5.9.15 Segment 5 wedge resection	N/Y
5.9.16 Segment 6 wedge resection	N/Y
5.9.17 Segment 7 wedge resection	N/Y
5.9.18 Segment 8 wedge resection	N/Y
5.9.19 Anatomical resection segment 1	N/Y
5.9.20 Anatomical resection segment 2	N/Y
5.9.21 Anatomical resection segment 3	N/Y
5.9.22 Anatomical resection segment 4	N/Y
5.9.23 Anatomical resection segment 5	N/Y
5.9.24 Anatomical resection segment 6	N/Y
5.9.25 Anatomical resection segment 7	N/Y
5.9.26 Anatomical resection segment 8	N/Y
5.10 Liver transplantation	N/Y
5.10.1 As primary treatment	N/Y
5.10.2 After other surgical procedures	N/Y
PANCREAS	
5.11 Pancreas resection	N/Y
5.11.1 Pancreatoduodenectomy	N/Y
5.11.2 Distal pancreatectomy	N/Y
5.11.3 Total pancreatectomy	
5.11.4 Central pancreatectomy	N/Y
5.11.5. Enucleation	
BILE DUCT	
5.12.1 Cholecystectomy	N/Y
5.12.2 Bile duct resection plus hepaticojejunostomy	N/Y
5.12.3 Intraoperative cholangioscopy	N/Y
5.12.4 Intraoperative cholangiography	N/Y
5.12.5. Other	Text

6. POST-OPERATIVE COURSE	
6.1 Intensive Care Unit admission	N/Y
6.2 Lenght of ICU stay	Days
6.3 Date of discharge home	dd/mm/yyyy
6.4 Length of hospital stay	Days
6.5 Post-operative complication during initial hospitalization (Clavien- Dindo)	(I/II/III/IV/V/Unknown)
6.5.1 If Clavien-Dindo V, answer this	
6.5.1.1 Date of death	dd/mm/yyyy
6.5.2 Bile leakage	No bile / Grade A / Grade B / Grade C
6.5.3 Liver failure	No failure / Grade A / Grade B / Grade C
6.5.4 Postoperative hemorrhage	None / Grade I /Grade II /Grade III
6.5.5 Pancreatic fistula	No fistula / Grade A / Grade B / Grade C
6.5.6 Delayed gastric emptying	No DGE/ Grade A / Grade B / Grade C
6.5.7 Other complications	N/Y
6.5.7.1 Cardiac arrest	N/Y
6.5.7.2 Pulmonary embolism	N/Y
6.5.7.3 Stroke (CVA/TIA)	N/Y
6.5.7.4 Abdominal abscess	N/Y
6.5.7.5 Pneumonia	N/Y
6.5.7.6 Urinary tract infection	N/Y
6.5.7.7 Other	N/Y
6.5.7.8 None	N/Y
6.6 Re-intervention	N/Y
6.6.1 Type of re-intervention	Radiologic / Endoscopic / Surgical
6.6.2 Reason for re-intervention	Free text
6.7 Reason for ICU re-admission	Free text
6.7.1 Length of re-admission ICU	Days
6.8 Readmission within 90 days	N/Y
6.8.1 If yes, date of readmission	dd/mm/yyyy
6.8.2 If yes, reason for re-admission	Free text
6.8.3 Lenght of re-hospitalization	Days
6.9 Reoperation within 90 days	N/Y
6.9.1 If yes, date reoperation	dd/mm/yyyy
7. HISTOPATHOLOGICAL DETAILS	
7.1 Location	Liver/Biliary/pancreas (multiple choice)
7.1.1 Multiple/unique	
7.2 Diameter of lesion (bigger)	mm
7.3 Resection status (Royal College Pathologists)	
7.3.1 R0-microscopically radical, margin ≥ 1mm	N/Y
7.3.2 R1-microscopically margin < 1mm	N/Y
7.3.3 R2-macroscopically	N/Y
7.3.4 Unknown	N/Y
7.4 Histological degree	
7.4.1. Low grade dysplasia	N/Y
7.4.2. High grade dysplasia	N/Y
7.4.3. Adenoma	N/Y
7.4.4. Carcinoma in situ	N/Y
7.4.5. Invasive carcinoma	
7.5 Histological type	Intestinal/pancreatobiliary/gastric/oncocytic
7.6 Immuno Histochemical study	
7.7 Mucin	
7.8 BillN	Free text
7.9 Luminal communication with adjacent bile duct	
7.10 Stromal invasion	
7.11 Vascular invasion	

7.12 Lymphatic invasion	
7.13 Perineural invasion	
7.14 Neuroendocrine differenciation	
7.15 T (1/2/3/4)	
7.16 Lymph nodes harvested	
7.17 Lymph nodes involved	
7.18 Cystic duct margin	
7.19 Bile duct margin	
7.20 Paremchymal margin	
8. FOLLOW UP-ADJUVANT THERAPY AND SURVIVAL POST-DISCHARGE	
8.1 Date of last follow up	MM/YYYY
8.2 Alive Y/N	N/Y
8.2.1. Date of death	
8.3 Liver relapse	N/Y
8.4 Pancreas relapse	N/Y
8.5 Extra-hepatic metastasis relapse	N/Y
8.5.1 If yes, which organ affected	Free text
8.5 Adjuvant chemotherapy	N/Y
8.5.1 If yes, date last adjuvant therapy	
8.5.2 Number of subsequent systemic treatment lines until death	dd/mm/yyyy
8.6 Re-surgery as rescue	N/Y
8.6.1 Which surgical procedure?	Text
8.7 Liver transplantation as rescue	N/Y

Appendix 2

Short survey on standards of care

DATA COLLECTION QUESTIONS

1. Please provide the name and contact details of the local study coordinator at your institution:
    1. First name
    2. Initial(s)
    3. Last name
    4. Academic title/ degree
    5. Job title
    6. Institution name
    7. Department
    8. Institution address
    9. City
    10. Postal code
    11. Province
    12. Country
    13. Email address
    14. Phone number (incl. country code)

2. Has your institution performed any surgical procedures for IPNB between 2010 - 2020 (Yes/No)

3. Please state who was responsible for the data collection in this study? (e.g. medical student supervised by a surgeon; PhD candidate / research fellow; dedicated resident / clinical fellow; surgeon). (Multiple choice)

4. Please state how collection of preoperative, perioperative, and postoperative variables was performed:
    1. Prospectively maintained database.
    2. Retrospective medical record review of digital records.
    3. Retrospective medical record review of paper records.
    4. Other.

SURGICAL EXPERTISE QUESTIONS

5. Please provide the number of bile duct resections (all indications but not PD) at your institution for the period of study (2010-2020).

6. Please provide the number of liver resections (all indications) at your institution for the period of study (2010 – 2020).

7. Please provide the number of liver transplantations (all indications) at your institution for the period of study (2010-2020).

8. Would you be interested in participating in a retrospective international study?

9. If so, would you be interested in participating in a follow-up prospective international study?

Appendix 3

Classifications

1) Charlson Comorbidity Index *(Roffman C, Buchanan J, Allison G.T. Charlson Comorbidities Index. J Physiother. 2016; 62(3): 171).*

COMORBIDITY	SCORE
Prior myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1
Cerebrovascular (hemiplegia) event	1
Moderate- severe renal disease	1
Diabetes with chronic complications	2
Cancer without metastases	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired immuno- deficiency syndrome (AIDS)	6

2) Intra-operative events Satava classification *(Satava RM. Identification and reduction of surgical error using simulation. Minim Invasive Ther Technol. 2005; 14:257–261).*

SATAVA CLASSIFICATION	DESCRIPTION
None	No events.
Grade 1	Excessive blood loss, damage to surrounding structures (not requiring conversion).
Grade 2	Conversion or major change to planned operation.
Grade 3	Intra-operative death.

3) Surgical complications. Clavien- Dindo classification *(Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240(2): 205-13).*

CLAVIEN-DINDO	DESCRIPTION
Grade I	Any deviation from the normal preoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade IIIa	Surgical, endoscopic or radiological intervention that is not under general anesthesia.
Grade IIIb	Surgical, endoscopic or radiological intervention that is under general anesthesia.
Grade IVa	Life- threatening complication requiring intermediate care or intensive care unit management, single organ dysfunction (including dialysis, brain hemorrhage, isquemic stroke, and subarrachnoidal bleeding).
Grade IVb	Life- threatening complication requiring intermediate care or intensive care unit management, multi-organ dysfunction (including dialysis).
Grade V	Death of a patient.

4) The Royal College of pathologist. Histopathological resection *(The Royal College of Pathologists. Standards and Minimum Datasets for Reporting Cancers Minimum dataset for the histopathological reporting of pancreatic, ampulla of Vater and bile duct carcinoma. London R Coll Pathol. 2002).*

Resection	DESCRIPTION
Unknown	-
R0	Microscopically radical, margin ≥1mm.
R1	Microscopically irradical, margin <1 mm.
R2	Macroscopically irradical, positive margin.

5) Post-hepatectomy haemorraghe classification (ISGLS) *(Rahbari N, Garden J, Padbury R, Maddern G, Koch M, Hugh T, et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). HPB. 2011; 13(8): 528-35).*

ISGLS Haemorrhage	DESCRIPTION
None	-
A	PHH requiring transfusion of up to 2 units of PRBCs.
B	PHH requiring transfusion of >2 units of PRBCs but manageable without invasive intervention.
C	PHH requiring radiological interventional treatment (e.g. embolization) or re-laparotomy.

6) Post-hepatectomy bile leakage classification (ISGLS) *(Brooke M, Figueras J, Ullah S, Rees M, Vauthey JN, Hugh TJ, et al. Prospective evaluation of the International Study Group for Liver Surgery definition of bile leak after a liver resection and the role of routine operative drainage: an international multicentre study. HPB. 2015. 17(1):46-51).*

ISGLS Bile Leakage	DESCRIPTION
None	-
A	Bile leakage requiring no or little change in patients' clinical Management.
B	Bile leakage requiring a change in patients clinical Management (e.g additional diagnostic or interventional procederes) but manageable without a re-laparotomy. OR: a Grade A bile leakage lasting for >1 week.
C	Bile leakage requiring re-laparotomy.

7) Post-hepatectomy liver failure classification *(Rahbari N, Garden J, Padbury R, Brooke M, Crawford M, Ada R, et al. Posthepatectomy liver failure: a definition and grading by the international study group of liver surgery (ISGLS). Surgery. 2011. 149:713-724).*

ISGLS Liver Failure	DESCRIPTION
None	-
A	Liver failure with abnormal laboratory parameters, but not requiring change in the clinical management of the patient.
B	Liver failure resulting in change of usual clinical management, but manegeable without invasive treatment.
C	Liver failure resulting in change of usual clinical management requiring invasive treatment.

8) Pancreatic fistula *(Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-Del Castillo C, Fingerhut A, Friess H, Gouma DJ, Hackert T, Izbicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande SV, Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M; International Study Group on Pancreatic Surgery (ISGPS). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017 Mar;161(3):584-591).*

Pancreatic fistula	Grade A	Grade B	Grade C
Clinical conditions	Well	Often well	Ill appearing/bad
Specific treatment antibiotics, total parenteral nutrition, somatostatin analogues	No	No/yes	Yes
US/CT (if obtained)	Negative	Negative/positive	Positive
Persistent drainage after 3 weeks	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to postoperative pancreatic fistula	No	No	Possibly yes
Signs of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

Modified after Bassi et al. [6].

9) Delayed gastric emptying *(Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007 Nov;142(5):761-8).*

DGE grade	No DGE	Grade A	Grade B	Grade C
Gastric tube removed on POD	≤3	4-7	8-14	≥15
Gastric tube reinserted anytime after POD	None	>3	>7	>14
Unable to tolerate solid oral diet by POD	−	7-13	14-20	≥21
Vomiting/gastric distension	−	±	+	+
Use of prokinetics	−	±	+	+
Nutritional support (enteral or parenteral)	−	±	+	+
Associate of postoperative complication	−	±	+	+
Diagnostic evaluation (endoscopy, UGI, and CT)	−	−	±	+