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-Martínez, MD[j], George N. Tzimas, MD, MSc, PhD, FACS[ee], Sheraz Yaqub, MD[ff,gg], François Cauchy, MD[p], Mikel Prieto-Calvo, MD[f], Melroy A. D'Souza, MD[q], Harry V.M. Spiers, BSc, MBBS, MRCS[v,w], Marius C. van den Heuvel, MD[n], Ramón Charco, MD, PhD[c], Mickaël Lesurtel, MD, PhD[p], José M. Ramia, MD, PhD, FACS, FRCS, FRCS Ed[h,i]; on behalf of the Research and Scientific Committee of the E-AHPBA

[a]*Division of Hepatobiliary and Pancreas Surgery, Miami Cancer Institute, Miami, Florida, USA,* [b]*Department of Surgery, Instituto de Investigación Sanitaria Aragón, Miguel Servet University Hospital, Zaragoza,* [c]*HPB Surgery and Transplantation, Hospital Universitario Vall d'Hebron,* [d]*Quirúrgica Cirujanos Asociados, Centro Médico Teknon, Barcelona,* [e]*Department of General, Visceral and Transplantation Surgery, Clinic and University Hospital Virgen de La Arrixaca, IMIB-ARRIXACA, Murcia,* [f]*Hepatobiliary Surgery and Liver Transplant Unit, Cruces University Hospital, Bilbao,* [g]*Department of General and Digestive Surgery, Hospital Doctor Peset, Valencia, Spain,* [h]*HPB Surgery and Liver Transplantation, Dr. Balmis General University Hospital, and Alicante Institute for Health and Biomedical Research (ISABIAL),* [i]*Miguel Hernández University, Alicante,* [j]*Servicio de Cirugía, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, Spain,* [k]*Department of General Surgery, Centro Hospitalar e Universitário de Coimbra,* [l]*Faculty of Medicine, University of Coimbra, Coimbra,* [m]*Department of Surgery, HEBIPA – Hepatobiliary and Pancreatic Unit, Hospital de Santo António, Centro Hospitalar Universitário do Porto, Porto, Portugal,* [n]*Department of HPB Surgery and Liver Transplantation, and Pathology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands,* [o]*Department of Digestive Surgical Oncology, Liver Transplantation Unit, CHU Besançon, Besancon,* [p]*Department of HPB Surgery and Liver Transplantation, Beaujon Hospital, Assistance Publique Hôpitaux de Paris, University of Paris Cité, Clichy, France,* [q]*Department of Clinical Science, Division of Surgery, Intervention and Technology, Karolinska Institutet, Karolinska University Hospital, Stockholm,* [r]*Department of Surgery, Lund University,* [s]*Skane University Hospital, Lund,* [t]*Department of Surgery in Linköping and Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden,* [u]*Department of Surgery, Transplantation and Gastroenterology, Semmelweis University, Budapest, Hungary,* [v]*Cambridge HPB Unit, Cambridge University Hospitals NHS Foundation Trust,* [w]*Department of Surgery, University of Cambridge, Cambridge,* [x]*Liver Transplant and HPB Surgery, Queen Elizabeth Hospital, Birmingham, UK,* [y]*Department of General and HPB Surgery, and Liver Transplantation, University Hospital Gent, Gent,* [z]*Department of Abdominal Surgery and Transplantation, CHU Liege, University of Liege,* [aa]*Department of Abdominal Surgery, CHC Groupe Santé, Liège, Belgium,* [bb]*HPB Clinical Unit, Gastrointestinal Surgery, Universitas Academic Hospital, University of the Free State, Bloemfontein,* [cc]*WITS University, Johannesburg, South Africa,* [dd]*Second Department of Propaedeutic Surgery, National and Kapodistrian University of Athens,* [ee]*Hepatobiliary Surgery Department, Hygeia Hospital, Athens, Greece,* [ff]*Department of HPB Surgery, Oslo University Hospital,* [gg]*Institute of Clinical Medicine, University of Oslo, Oslo, Norway and* [hh]*General Surgery Department, HPB Division, Nicosia General Hospital, Nicosia, Cyprus*

Mickaël Lesurtel and José M. Ramia should be considered joint senior authors.

Núria Lluís is the corresponding author during the review process.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: Department of Surgery, Division of Hepato-Pancreato-Biliary Surgery, Miguel Servet University Hospital, Paseo Isabel La Católica, 1-3, 50009 Zaragoza, Spain. Tel: +34 636 006 184; fax: + 34976765519. E-mail address: marioserradilla@hotmail.com (M. Serradilla-Martín) and Division of Hepatobiliary and Pancreas Surgery, Miami Cancer Institute, 8900 N Kendall Dr, Miami 33176, Florida USA. Tel: +1 786 774 2775. E-mail address: nurialluisv@gmail.com (N. Lluís).*

International Journal of Surgery (2023) 109:760–771

Received 31 August 2022; Accepted 19 January 2023

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.journal-surgery.net.

Published online 14 March 2023

http://dx.doi.org/10.1097/JS9.0000000000000280

Background/Purpose: Intraductal papillary neoplasm of the bile duct (IPNB) is a rare disease in Western countries. The main aim of this study was to characterize current surgical strategies and outcomes in the mainly European participating centers.
Methods: A multi-institutional retrospective series of patients with a diagnosis of IPNB undergoing surgery between 1 January 2010 and 31 December 2020 was gathered under the auspices of the European-African Hepato-Pancreato-Biliary Association. The textbook outcome (TO) was defined as a non-prolonged length of hospital stay plus the absence of any Clavien–Dindo grade at least III complications, readmission, or mortality within 90 postoperative days.
Results: A total of 28 centers contributed 85 patients who underwent surgery for IPNB. The median age was 66 years (55–72), 49.4% were women, and 87.1% were Caucasian. Open surgery was performed in 72 patients (84.7%) and laparoscopic in 13 (15.3%). TO was achieved in 54.1% of patients, reaching 63.8% after liver resection and 32.0% after pancreas resection. Median overall survival was 5.72 years, with 5-year overall survival of 63% (95% CI: 50–82). Overall survival was better in patients with Charlson comorbidity score 4 or less versus more than 4 ($P = 0.016$), intrahepatic versus extrahepatic tumor ($P = 0.027$), single versus multiple tumors ($P = 0.007$), those who underwent hepatic versus pancreatic resection ($P = 0.017$), or achieved versus failed TO ($P = 0.029$). Multivariable Cox regression analysis showed that not achieving TO (HR: 4.20; 95% CI: 1.11–15.94; $P = 0.03$) was an independent prognostic factor of poor overall survival.
Conclusions: Patients undergoing liver resection for IPNB were more likely to achieve a TO outcome than those requiring a pancreatic resection. Comorbidity, tumor location, and tumor multiplicity influenced overall survival. TO was an independent prognostic factor of overall survival.

Keywords: bile duct neoplasms, intraductal precursor lesion, pancreas, surgical resection, textbook outcome

Introduction

Intraductal papillary neoplasm of the bile duct (IPNB) accounts for 10–15% of bile duct tumors[1]. It is a macroscopic papillary epithelial lesion, similar to its counterpart intraductal papillary mucinous tumor of the pancreas, that grows into the lumen of intrahepatic and/or extrahepatic bile ducts[2]. The papillary growth of the IPNB can block the lumen of the bile ducts, sometimes generating cysts with mucous content and causing upstream dilatation[3]. Others are focal plaque-like lesions associated with bile duct strictures[4]. Multiple IPNB lesions can be found along the biliary tree[3]. The location is variable according to studies, ranging from 80% intrahepatic in some series to 70% extrahepatic in others[5], but they can be found synchronously or metachronically in both locations[6].

According to the degree of atypia, IPNB is classified into low-grade and high-grade, the latter being more frequent[2]. Depending on the type of epithelial cell, it is subclassified as intestinal, pancreatobiliary, gastric, or oncocytic, although several types may coexist[2]. The pancreatobiliary is the most frequent in Western countries, where it reaches 50%, while the intestinal one is more frequent in Asia[2,6]. A pioneering article found invasive carcinoma in three out of four patients with IPNB[7]. It is speculated whether IPNB is a precursor lesion of cholangiocarcinoma and whether the tumor that develops from IPNB has a better prognosis than other types of cholangiocarcinoma[7–9].

According to the 2019 WHO classification[5], IPNB can be subclassified into type I and type II. Type I is histologically similar to the pancreatic counterpart, without an invasive component or limited to less than 50% of the lesion area, and more frequently located in intrahepatic bile ducts. Type II has a more complex papillary architecture and is more frequent in extrahepatic bile ducts, although many tumors are difficult to classify into these subtypes[8].

Most publications on IPNB include patients from Asia, due to the higher incidence of IPNB in this geographic region compared to Western countries[8,10]. A considerable proportion of Asian patients with IPNB have hepatolithiasis or clonorchiasis[11]. Other risk factors include primary sclerosing cholangitis, biliary malformations, and familial adenomatous polyposis/Gardner syndromes[6]. In Western countries, most IPNBs are sporadic[6]. As a rare condition, few patients with IPNB are treated in Western countries, even in centers with a special dedication to hepato-pancreato-biliary (HPB) surgery such as those participating in the present study. Recently, the term textbook outcome (TO) has been used to define a composite measure of quality that reflects hospital performance more reliably than individual measures. It is intended to be a reflection of the so-called ideal outcome[12–14]. It has been reported that patients treated in dedicated cancer centers are more likely to experience a TO after HPB surgery[13]. The aim of this study was to describe disease characteristics, surgical outcomes, and survival in patients with IPNB in participating centers. Secondary endpoints were to examine TO achievement and identify factors associated with survival in this setting.

HIGHLIGHTS

- Intraductal papillary neoplasia of the bile duct is a rare disease in Western countries.
- This European study examined the outcomes of 85 patients operated on for this tumor.
- Comorbidity, tumor location, and tumor multiplicity influenced overall survival.
- Textbook outcome achievement rate was higher after hepatic than pancreatic resection.
- Textbook outcome was a prognostic factor of overall survival.

Patients and methods

Study design

This is an observational retrospective study of patients with IPNB lesions undergoing elective HPB surgery between 1 January 2010 and 31 December 2020 at centers represented by members of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA). The ethics committee of the Vall d'Hebron Hospital,

Barcelona, Spain, approved the study protocol on 2 December 2021 and waived the informed consent of patients due to the retrospective nature of the study (PR[AG]469/2021). The study is registered at https://www.researchregistry.com/ with the unique identification number (UIN) 8223. An invitation to participate in the study was sent to European members of E-AHPBA affiliated with HPB and liver transplantation centers. The steering committee agreed with the participating investigators that the cases to be included in the study should be in accordance with the definitions and terms applicable to IPNB published in the WHO 2019 tumor classification, which was included as a reference in the study protocol[5]. It was left to each participating center the responsibility of reviewing the pathology and all relevant data before recruiting the patient for the study. Planning and analysis of the study were carried out according to the STROCCS Reporting Guidelines for Cohort Studies[15].

Demographics, baseline characteristics, and diagnosis

In addition to demographic data and past surgical history, BMI, American Society of Anesthesiology (ASA) score, Eastern Cooperative Oncology Group performance status, Charlson Comorbidity Index (CCI)[16], biliary symptoms, serum bilirubin and CA-19.9 level, and presence of hepatolithiasis or *Clonorchis* infestation were recorded. The contribution of preoperative imaging tests [computed tomography (CT), MRI, transabdominal ultrasonography, endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography, endoscopic cholangioscopy, percutaneous transhepatic cholangiography] used to identify IPNB lesions was assessed.

Intraoperative events and surgical procedures

The surgical approach, as well as operative time, estimated blood loss, and need for transfusion, were recorded. The finding of intraluminal mucin, both intraoperatively and in the pathology specimen, was also recorded. Intraoperative events were graded according to the Satava classification[17]. The type of biliary resection and reconstruction was recorded, as well as whether intraoperative cholangioscopy or cholangiography was used. When hepatic resection was performed, clamping time was recorded if Pringle's maneuver was used. The reason for optional liver transplantation was specified. The type of resection was specified if a pancreatectomy was performed.

Postoperative course

Length of ICU and hospital stay, and 90-day morbidity and mortality according to the Clavien–Dindo classification were recorded[18]. Bile leak[19], posthepatectomy liver failure[20], postoperative hemorrhage[21], pancreatic fistula[22], and delayed gastric emptying[23], according to International Study Group of Liver Surgery or International Study Group of Pancreatic Surgery, and other major medical complications were identified. Any additional procedures (radiological, endoscopic, or surgical) performed during the index hospitalization, episodes of ICU readmission, hospital readmission, or reintervention during the first 90 days were recorded.

Pathology

The number and diameter of the lesions and their intrahepatic or extrahepatic location were identified, the latter cranial or caudal to the confluence of the cystic duct. In addition to the tumor stage, the number of lymph nodes harvested and invaded was recorded. The degree of dysplasia was graded low or high according to the criteria used for intraepithelial lesions of the pancreatobiliary tract[24]. The epithelial cells were classified as gastric, oncocytic, pancreatobiliary, or intestinal[8,11]. Additional features included the presence of intraluminal mucin, biliary intraepithelial neoplasia (BilIN), stromal, vascular, lymphatic, or perineural invasion, and neuroendocrine differentiation. Local communication with the bile ducts was evidenced by the presence of BilIN within the adjacent bile ducts, or of peribiliary glands in the cystic wall if an adjacent cyst was identified[25]. Involvement of the resection margin of the cystic duct, common bile duct, and parenchyma was examined[26].

TOs

The TO was defined based on the absence of all of the following: prolonged length of hospital stay (a length of hospital stay $\geq$ 75th percentile of the total cohort), 90-day Clavien–Dindo grade at least III complications, 90-day readmission, and 90-day mortality[13]. When all these components together did not occur, the patient was labeled as having experienced a TO.

Local or systemic treatment and follow-up

Modalities and doses of adjuvant chemotherapy and radiotherapy were recorded. Dates of recurrence, last follow-up, and death were identified.

Data collection

Each participating center designated a person responsible for collecting the information, in contact with the study coordinators and data management coordinator. Anonymized data were collected and managed using REDCap tools (REDCap, Research Electronic Data Capture, University of Vanderbilt, Nashville, Tennessee, USA) hosted at Asociación Española de Gastroenterología (AEG; https://www.redcap.aegastro.es)[27].

Analysis

Descriptive statistics were used for the demographic and baseline characteristics of patients. Quantitative variables are reported as the median and interquartile range (IQR), and categorical variables as absolute and relative frequencies. Differences between groups of patients were compared using the χ^2 test or Fisher's exact test for categorical data, the t test for parametric quantitative data, and the Mann–Whitney U test for quantitative nonparametric data. Cohen's κ coefficient was used to describe and measure interobserver diagnostic agreement (i.e. imaging or surgery versus pathology). The contribution of each of the four components to the achievement of TO was calculated for all patients, and separately for liver and pancreas surgery. In addition, the cumulative TO achievement was calculated by combining the individual contributions. Multivariable logistic regression analysis was used to determine whether there was an association between demographic and clinical characteristics of patients or pathologic characteristics of tumors and achievement of TO. The characteristics corresponding to the highest proportion of patients were selected as a reference. Overall survival was defined as the timeframe between the date of surgery and the date of death or last follow-up. Progression-free survival was defined

by the interval between the date of surgery and the date of recurrence diagnosis or last follow-up or death in patients without recurrence[28]. Survival curves were constructed by the Kaplan–Meier method and were compared using the log-rank test. A multivariable Cox proportional hazards regression model was used to identify prognostic factors associated with survival. All variables that were significant at 0.10 on univariable analysis were entered into a multivariable model. *P* values of less than 0.05 were considered statistically significant. All analyses were performed using RStudio, version 1.2.5001 (Integrated Development for R; RStudio, Inc., Boston, Massachusetts, USA).

Results

Demographic and baseline characteristics

A total of 28 centers contributed 85 patients who underwent surgery for IPNB between 1 January 2010 and 31 December 2020, with a median (IQR) of 2 (1–4) patients per center (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JS9/A119). Demographics and baseline characteristics are presented in Table 1. The median age of patients was 66 years (55–72); 49.4% were women, 87.1% Caucasian, with a BMI of 25.8 (23.1–28.2). Most had ASA score II (61.2%) and Eastern Cooperative Oncology Group performance status 0 (57.6%). Patients had a median CCI score of 4 (2–5) and an estimated median 10-year survival of 53% (21–77). One-third of patients (35.3%) had a history of abdominal surgery, and a few had a history of liver disease. Abdominal pain, jaundice, and cholangitis were the main symptoms. Bilirubin was elevated, and CA-19.9 was mostly within normal limits. Hepatolithiasis was found in two (2.4%) patients and *Clonorchis* infestation in none.

Table 1

Demographic and baseline characteristics.

	Patients, $n = 85$
Age, years, median (IQR)	66 (55–72)
Gender, *n* (%)	
Male	43 (50.6)
Female	42 (49.4)
Ethnicity, *n* (%)	
Asian	3 (3.5)
Caucasian	74 (87.1)
African	4 (4.7)
Latin	4 (4.7)
BMI, kg/m^2, median (IQR)	25.8 (23.1–28.2)
ASA score, *n* (%)	
I	12 (14.1)
II	52 (61.2)
III	20 (23.5)
IV	0
V	0
Unknown	1 (1.2)
ECOG performance status, *n* (%)	
0	49 (57.6)
1	30 (35.3)
2	6 (7.1)
3	0
4	0
Charlson Comorbidity Index (CCI)	
Score, median (IQR)	4 (2–5)
Estimated 10-year survival, %, median (IQR)	53 (21–77)
Past surgical history, *n* (%)	30 (35.3)
Cholecystectomy[a]	13 (15.3)
Liver resection[a]	1 (1.2)
Pancreatic resection[a]	0
Bile duct surgery[a]	2 (2.4)
Other supramesocolic surgery[a]	1 (1.2)
Inframesocolic surgery[a]	11 (12.9)
Past medical history – liver related, *n* (%)	
Primary biliary cirrhosis[a]	1 (1.2)
Autoimmune hepatitis[a]	2 (2.4)
Primary sclerosing cholangitis[a]	3 (3.5)
Alcohol-related cirrhosis[a]	0
Hepatitis B virus[a]	2 (2.4)
Hepatitis C virus[a]	0
Other[a]	4 (4.7)
Preoperative symptoms, *n* (%)	
Asymptomatic[a]	22 (25.9)
Abdominal pain[a]	34 (40.0)
Jaundice[a]	38 (44.7)
Acute cholangitis[a]	19 (22.4)
Preoperative lab, median (IQR)	
Bilirubin, mg/dl	4.3 (1–9)
CA-19.9, U/ml	19 (6.0–63.7)
Associated conditions, *n* (%)	
Hepatolithiasis	2 (2.4)
Clonorchis infestation	0

[a]Items with multiple possible answers.

ASA, American Society of Anesthesiology; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

Preoperative work-up and management

A representative MRI image of an IPNB is shown in Supplementary Figure 1a, Supplemental Digital Content 1, http://links.lww.com/JS9/A119. Preoperative imaging tests, their diagnostic performance, and imaging findings are summarized in Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/JS9/A119. As an example, the diagnostic sensitivity of CT and MRI was only 17.3 and 35.5%, respectively. Slightly more than half of the patients (55.3%) had intrahepatic IPNB. Imaging tests detected extrahepatic IPNB involving the bile duct upstream of the confluence with the cystic duct in 26 patients (30.6%) and/or distal in 32 patients (37.6%), and pancreatic involvement in 11 patients (12.9%). Imaging tests detected a single tumor in 67 patients (78.8%), multifocal in 18 (21.2%), and a size of 20 mm (15.5–30.0) for the largest tumor (missing size data for 22 patients). In 21 patients (24.7%), a preoperative biopsy compatible with IPNB was obtained. Preoperative biliary drainage was performed in 29 patients, endoscopically in 24, and percutaneously via transhepatic access in five.

Intraoperative details and surgical procedures

An open approach was performed in 72 patients (84.7%) and a laparoscopic approach in 13 (15.3%) (Table 2). An intraoperative event was recorded in seven patients (8.3%), including excessive blood loss in five, and conversion or major change to planned operation in two. No intraoperative deaths occurred. Intraluminal mucin was seen in 18 patients (21.2%). Median operative time was 357 min (254–428). Median estimated intraoperative blood loss was 300 ml (163–500), and intraoperative transfusion was administered to 18 patients (21.2%), who received a median of two (2–3) pRBC (packed red blood cells) units. Liver resection was performed in 49 patients (57.6%).

Table 2

Intraoperative details and surgical procedures.

	Patients, $n = 85$
Surgical approach, *n* (%)	
Open	72 (84.7)
Laparoscopic	13 (15.3)
Intraoperative events (Satava), *n* (%)	
No intraoperative events	78 (91.8)
Excessive blood loss, damage (no conversion)	5 (5.9)
Conversion or major change to the planned operation	2 (2.4)
Intraoperative death	0
Intraluminal mucin, *n* (%)	18 (21.2)
Operative time, min, median (IQR)	357 (254–428)
Estimated blood loss, ml, median (IQR)	300 (163–500)
Perioperative pRBC transfusion, *n* (%)	18 (21.2)
pRBC units transfused, median (IQR)	2 (2–3)
Liver resection, *n* (%)	49 (57.6)
Type of liver resection, *n* (%)	
Atypical/nonanatomical[a]	3 (3.5)
Left lateral sectionectomy (2 and 3)[a]	4 (4.7)
Left hemihepatectomy (2, 3, and 4)[a]	26 (30.6)
Right hemihepatectomy (5, 6, 7, and 8)[a]	5 (5.9)
Extended right hepatectomy (4, 5, 6, 7, and 8)[a]	5 (5.9)
Extended left hepatectomy (2, 3, 4, 5, and 8)[a]	2 (2.4)
Segment 4 wedge resection[a]	2 (2.4)
Segment 5 wedge resection[a]	1 (1.2)
Anatomical resection segment 1[a]	11 (12.9)
Liver transplantation, *n* (%)	5 (5.9)
Pancreas resection, *n* (%)	
Pancreatoduodenectomy	26 (30.6)
Total pancreatectomy	1 (1.2)
Bile duct procedures, *n* (%)	
Cholecystectomy[a]	61 (71.8)
Bile duct resection + hepaticojejunostomy[a]	53 (62.4)
Intraoperative cholangioscopy[a]	5 (5.9)
Intraoperative cholangiography[a]	6 (7.1)
Other bile duct surgical procedure[a]	5 (5.9)

[a]Items with multiple possible answers.
pRBC, packed red blood cells.

Table 3

Postoperative course.

	Patients, $n = 85$
ICU admission, *n* (%)	53 (62.4)
Length of ICU stay, days	2 (1–5)
Length of hospital stay, days	11 (6–20)
90-day postop complications, Clavien–Dindo, *n* (%)	
I	37 (43.5)
II	20 (23.5)
III-a	11 (12.9)
III-b	6 (7.1)
IV-a	2 (2.4)
IV-b	3 (3.5)
V	6 (7.1)
Bile leak, *n* (%)	13 (15.3)
Grades A/B/C	3/5/5
Liver failure, *n* (%)	7 (8.2)
Grades A/B/C	2/3/2
Postoperative hemorrhage, *n* (%)	12 (14.1)
Grades I/II/III	3/2/7
Postoperative pancreatic fistula, *n* (%)	13 (15.3)
Biochemical leak/grades B/C	4/7/2
Delayed gastric emptying, *n* (%)	17 (20.0)
Grades A/B/C	6/9/2
Other complications, *n* (%)	
Cardiac arrest	1 (1.2)
Pulmonary embolism	2 (2.4)
Stroke	1 (1.2)
Intraabdominal abscess	10 (11.8)
Urinary tract infection	2 (2.4)
Additional procedures during initial hospitalization, *n* (%)	14 (16.5)
Radiological/endoscopic/surgical	6/2/9
ICU readmission, *n* (%)	7 (8.2)
Length of ICU readmission, days, median (IQR)	12 (7–19)
Hospital readmission within 90 days, *n* (%)	17 (20.0)
Length of stay during readmission, days, median, *n* (IQR)	7 (3–12)
Reoperation within initial 90 days, *n* (%)	12 (14.1)

IQR, interquartile range.

The types of liver resection are detailed in Table 2. Liver transplantation was performed in five patients (5.9%), in two as the primary treatment, and in three as a salvage surgical procedure. Pancreatoduodenectomy was performed in 26 patients (30.6%), total pancreatectomy in one (1.2%). Bile duct procedures are detailed in Table 2.

Postoperative course

After surgery, 53 patients (62.4%) spent 2 days (1–5) in the ICU (Table 3). The median length of hospital stay was 11 days (6–20). Postoperative complications at 90 days according to Clavien–Dindo, specific complications (bile leak, liver failure, hemorrhage, pancreatic fistula, delayed gastric emptying), other complications, and other procedures performed during the index hospitalization, are detailed in Table 3. In the first 90 postoperative days, a Clavien–Dindo grade at least III complication occurred in 32.9% of patients, mortality was 7.1%, 17 patients (20.0%) were readmitted to the hospital for 7 days (3–12), and 12 patients (14.1%) underwent reoperation. Twelve patients received a median of six cycles (6–9) of adjuvant chemotherapy (capecitabine 7, FOLFIRINOX 1, FOLFIRI 1, unknown 3), and two patients received adjuvant external beam radiation therapy. The most used imaging techniques for surveillance were CT (59.3%) and MRI (27.9%).

Pathology report

A representative photomicrograph of an IPNB is shown in Supplementary Figure 1b, Supplemental Digital Content 1, http://links.lww.com/JS9/A119. Pathology data are shown in Table 4. According to pathology reports, 44 patients (51.8%) had intrahepatic IPNB; extrahepatic IPNB involving the bile duct was present cranial to the confluence with the cystic duct in 27 patients (31.8%) and/or caudal in 31 patients (36.5%). Pathology reports showed a single tumor in 65 patients (76.5%), multiple tumors in 20 patients (23.5%), and a size of 20 mm (15–33) for the largest lesion. Mucin was found in 27 patients (31.8%). Agreement between imaging and pathology for tumor location was near perfect ($\kappa = 0.88$), and there was substantial agreement between imaging and pathology for tumor multiplicity ($\kappa = 0.80$), and between surgery and pathology regarding the presence of intraluminal mucin ($\kappa = 0.61$) (Supplementary Table 3, Supplemental Digital Content 1, http://links.lww.com/

Table 4

Pathology report.

	Patients, $n = 85$
Localization of the lesion(s), *n* (%)	
Intrahepatic[a]	44 (51.8)
Extrahepatic above the cystic duct[a]	27 (31.8)
Extrahepatic below the cystic duct[a]	31 (36.5)
Number of lesions, *n* (%)	
Single	65 (76.5)
Multiple	20 (23.5)
Diameter of the largest lesion, mm, median (IQR)	20 (15–33)
Presence of mucin, *n* (%)	27 (31.8)
Local communication with the adjacent bile duct, *n* (%)	43 (50.6)
Biliary intraepithelial neoplasia (BilIN), *n* (%)	
BilIN-1	14 (16.5)
BilIN-2	6 (7.1)
BilIN-3	4 (4.7)
Unknown	61 (71.8)
Degree of atypia, *n* (%)	
Low-grade dysplasia	21 (24.7)
High-grade dysplasia	14 (16.5)
Adenoma	3 (3.5)
Carcinoma *in situ*	11 (12.9)
Invasive carcinoma	36 (42.4)
Type of epithelial cells, *n* (%)	
Intestinal	17 (20.0)
Pancreatic-biliary	59 (69.4)
Gastric	8 (9.4)
Oncocytic	1 (1.2)
T stage, *n* (%)	
Tis	38 (44.7)
T1	21 (24.7)
T2	20 (23.5)
T3	4 (4.7)
T4	0
NA	2 (2.4)
Invasion, *n*, yes/no/unknown	
Stromal	16/59/10
Vascular	9/69/7
Lymphatic	9/64/12
Perineural	13/62/10
Neuroendocrine differentiation, *n*, yes/no/unknown	1/67/17
Resection margin status, *n* (%)	
R0	69 (81.2)
R1	14 (16.5)
R2	1 (1.2)
Unknown	1 (1.2)
Resection margin positive, *n* (%)	
Cystic duct[a]	3 (3.5)
Common bile duct[a]	9 (10.6)
Parenchymal[a]	4 (4.7)
Lymph nodes harvested	
Patients, *n* (%)	61 (71.8)
Number, median (IQR)	6 (2–16)
Lymph nodes affected	
Patients, *n* (%)	11 (12.9)
Number, median (IQR)	3 (2–4)

[a]Items with multiple possible answers.
IQR, interquartile range.

JS9/A119). BilIN, postulated as a precursor of bile duct carcinoma, was found in adjacent bile ducts of 24 patients. Most patients had tumors with epithelial cells of the pancreatobiliary type (69.4%). Finally, Tis was diagnosed in 38 patients (44.7%). Stromal, vascular, lymphatic, perineural invasion, or neuroendocrine differentiation was found in 16, 9, 9, 13, and 1 patients, respectively. Most resections were R0 (81.2%), and incomplete resections were distributed among the resection margins of the cystic duct, common bile duct, or parenchyma. A median of six lymph nodes (2–16) per patient was harvested from 61 patients (71.8%). In 11 of these patients, a median of three (2–4) involved lymph nodes per patient was identified.

TOs

To define TO, the 75th percentile of length of hospital stays (20 days) was chosen. Overall, TO was achieved in 46 of 85 patients (54.1%), a figure that varied according to the type of surgery: it reached 63.8% in liver surgery and 32.0% after pancreas resection (Fig. 1). Patients more likely to experience TO had a lower CCI score (TO, 3.5 [2–4]; non-TO, 4 [3–5]; $P = 0.01$) and a higher estimated 10-year survival (TO, 53% [53–90]; non-TO, 53% [21–77]; $P = 0.03$). Patients who underwent pancreas resection were less likely to achieve a TO (TO, 17.4%; non-TO, 48.7%; $P = 0.004$) (Supplementary Table 4, Supplemental Digital Content 1, http://links.lww.com/JS9/A119). Multivariable analysis showed that pancreas resection (OR: 0.27; 95% CI: 0.09–0.74; $P = 0.01$) was an independent predictor factor of low TO achievement.

Survival analysis

Median follow-up was 23 months (14–37.7). During the follow-up period, 22 patients (25.9%) died. Median overall survival was 5.72 years [95% CI: 4.19–not reached (NA)] (Fig. 2A). Actual overall survival at 1, 3, 5, and 10 years were 92% (95% CI: 86–98), 73% (95% CI: 61–86), 63% (95% CI: 50–82), and 31% (95% CI: 12–81), respectively. Recurrence was detected in 16 patients, single location in eight and multiple in eight; the liver was affected in 11 patients, bile ducts and pancreas in one, respectively, and other locations in seven (lung, peritoneum, supradiaphragmatic and infradiaphragmatic lymph nodes, and duodenum). Median progression-free survival was not reached (95% CI: 6.60–NA) (Fig. 2B). Actual progression-free survival at 1, 3, 5, and 10 years were 90% (95% CI: 82–98), 75% (95% CI: 62–91), 75% (95% CI: 62–91), and 57% (95% CI: 31–100), respectively. Recurrence was treated in 15 patients (curative intent in four, palliative intent in 11); 12 of these patients received chemotherapy and three underwent surgery.

Overall survival comparisons using log-rank analysis are shown in Figure 3. Overall survival was better in patients with a CCI score 4 or less compared to patients with a CCI score more than 4 ($P = 0.016$), in patients with intrahepatic tumor compared to patients with extrahepatic tumor ($P = 0.027$), in patients with a single tumor compared to patients with multiple tumors ($P = 0.007$), in patients who underwent liver resection compared with those who underwent pancreatic resection $P = 0.017$), and in patients who achieved TO compared with those who failed ($P = 0.029$). There was no difference in overall survival according to the presence of mucin, degree of atypia, epithelial cell type, T stage, or resection margin status. Analysis of the subgroup of patients who had undergone lymph node dissection showed that the finding of positive lymph nodes was associated with worse overall and progression-free survival (Fig. 4).

Multivariable Cox analysis showed that not achieving TO (HR: 4.20; 95% CI: 1.11–15.94; $P = 0.03$) was an independent

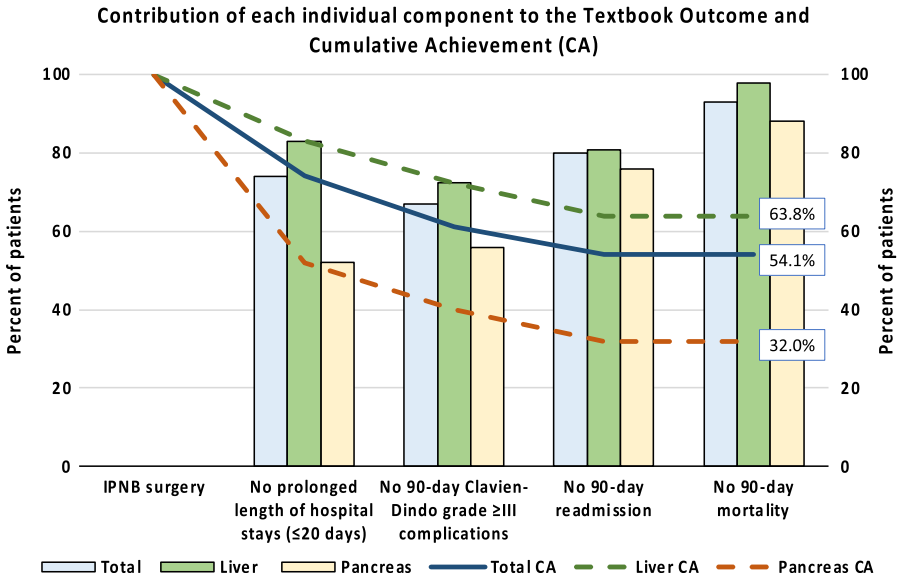

Figure 1. Textbook outcome (TO) for all patients (blue bars), and patients stratified into liver (green bars) and pancreas (yellow bars) surgery for IPNB. The contribution of each individual component (horizontal axis) to the TO (bars) and to the cumulative achievement (lines) are represented in percentages (vertical axes). The labels indicate the final cumulative TO (in percentage) in each subgroup. IPNB, intraductal papillary neoplasm of the bile duct.

risk factor of poor overall survival (Table 5 and Supplementary Table 5, Supplemental Digital Content 1, http://links.lww.com/JS9/A119). No independent predictor of progression-free survival was identified on multivariable analysis (Supplementary Table 6, Supplemental Digital Content 1, http://links.lww.com/JS9/A119).

Discussion

In summary, IPNB is a rare disease in Western countries. Over half (54.1%) of patients experienced a TO after IPNB resection, a proportion that was higher after hepatic resection (63.8%) and lower after pancreatic resection (32.0%). Median overall survival was 5.72 years, and 5-year overall survival was 63%. TO was an independent prognostic factor of overall survival.

To our knowledge, this multicenter study is the largest in a number of centers and patients to date to provide data on the surgical management of IPNB in Europe. Participating centers are most likely the ones to receive IPNB referrals as they perform complex HPB surgery and even liver transplantation. Unlike the Asian series, 87.1% of the patients in the present series were Caucasian, only two had hepatolithiasis, and none had *Clonorchis* infection. There were no significant gender differences. Little is known regarding the etiology of IPNB in Western countries. An early series from the Memorial Sloan Kettering Center in New York identified a predominance of the pancreatobiliary subtype, with invasive carcinoma found in 74% of patients[7]. Both characteristics seem to stand the test of time in recent publications[2]. On the other hand, the oncocytic subtype seems to be more frequent in Western populations[11], although it was a minority in our series. Indeed, IPNBs identified in the West are more likely to be extrahepatic and invasive[29]. While in Asia many cases are associated with flukes and stones, most IPNBs in Western countries are sporadic[6] and diagnosed in patients who are primarily of non-Asian descent. IPNB may be both a rare disease and an underdiagnosed disease in the West[30]. Taken together, the limited evidence available suggests that there are histopathological differences in IPNB between Western and Asian populations, which may reflect differences in underlying etiological factors between the two geographic regions. Comparative studies are needed to delve into these differences.

The results of this European multicenter study have been assessed in comparison to the results of a published worldwide systematic review and meta-analysis that focused on the treatment of 391 patients with IPNB[29]. The clinical presentation of European patients was similar to the findings of the systematic review; the percentages of patients with pain, jaundice, cholangitis, or asymptomatic were in the ranges described[29]. There were differences in the imaging test findings, likely related to diagnostic habits in different geographical regions of the world. In the systematic review, it was found that the pancreaticobiliary cell subtype was more invasive[29]. In the present series, 69.4% of patients had a pancreaticobiliary subtype, but there were no differences in overall survival by epithelial cell type (intestinal, pancreatic-biliary, gastric/oncocytic) by log-rank analysis. The pathologist was ultimately responsible for labeling the lesion as intrahepatic or extrahepatic, the latter being above or below the cystic duct. IPNBs in Asia were found to be mostly intrahepatic and less invasive compared to Western countries[29]. In our series, half of the patients had intrahepatic IPNB, with better overall survival than extrahepatic IPNB by log-rank analysis. In the systematic review, 60% of the tumors were single and 40% multifocal[29]. In our series, 76.5% were single and 23.5% multiple. Finally, in the systematic review, 22% of patients underwent pancreatectomy as the only surgical procedure[29], while 31.8% of patients in our European series underwent pancreatectomy. Pancreatic resection was performed in patients with IPNB developing in the common bile duct below the cystic duct invading the pancreas, or in the intrapancreatic bile duct itself.

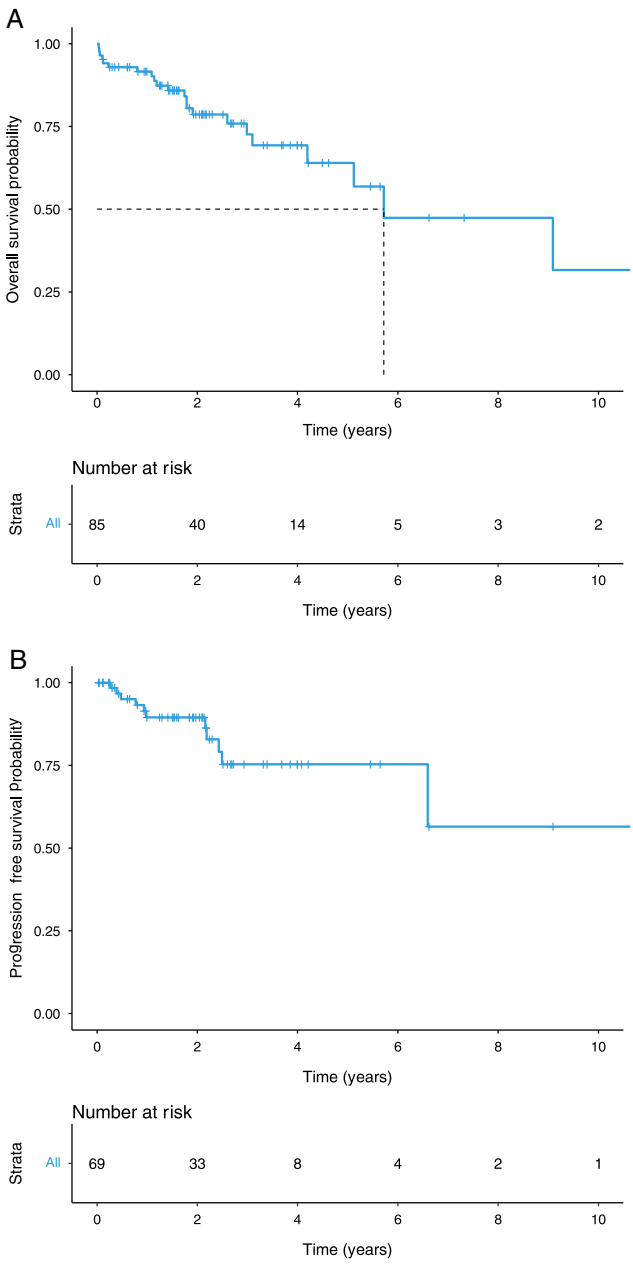

Figure 2. Overall survival (A) and progression-free survival (B) of patients who underwent surgery for intraductal papillary neoplasm of the bile duct depicted using the Kaplan–Meier curve. The dotted lines indicate median overall survival (median progression-free survival was not reached).

Exceptionally, one patient underwent total pancreatectomy. Intraoperative frozen examination showed invasion of the pancreatic resection margin after undergoing initial pancreaticoduodenectomy. In addition, the patient had atrophy of the body and tail of the pancreas and multiple enlarged regional lymph nodes. In fact, lymph node dissection harvested 25 lymph nodes, 11 of which were positive on definitive pathologic examination. The decision to perform a total pancreatectomy was made considering the extent of the resection and the high risk of pancreatic fistula in this patient[31].

To the best of our knowledge, the present study is the first to use the TO metric applied to the surgical treatment of patients with IPNB. The TO is a composite metric that simplifies comparison between groups and facilitates analysis of association. The median duration of postoperative hospital stay in our series was 11 days, lower than that reported in other similar series of IPNB patients[8]. We examined the TO of this European study in light of other published series on complex hepatobiliary surgery. Dedicated cancer centers in the U.S. used a minimally invasive approach in 17.0% of patients with hepatopancreatic cancer and reported that 48.8% of patients experienced TO[13]. Centers participating in our study used a minimally invasive approach in 15.3% and reported that 54.1% of patients experienced a TO. A study of Medicare administrative data in the U.S. showed that 44% of patients undergoing hepatopancreatic surgery experienced a TO[14]. However, the hospital-adjusted percentage was higher for patients undergoing liver surgery (16.6–78.8%) than for those undergoing pancreatic surgery (11.1–69.6%). Similarly, in our multicenter study, 63.8% of patients undergoing liver surgery experienced a TO, while the rate dropped to 32.0% for patients undergoing pancreatic surgery. In fact, pancreatic surgery was the only factor associated with TO on multivariable analysis in our study. Pancreas resection was associated with 73% decreased odds of TO achievement among patients who underwent surgical resection for IPNB. High morbidity associated with pancreatic-intestinal anastomosis (fistula, hemorrhage, infection) could explain the worse TO of pancreatic resection compared to hepatic resection[32]. Pancreatic duct diameter and pancreatic parenchyma texture, two characteristics associated with pancreatic fistula, were not recorded in our study. However, since the neoplasm was not pancreatic, it is tempting to speculate that most patients had a small-diameter duct and a soft pancreas, thereby increasing the risk of related complications. Likewise, length of hospital stay was a potential factor contributing to worse TO in pancreatic resection. Unlike a recent article on TO in pancreatic surgery[12], our study included length of hospital stay as a prerequisite for experiencing TO. The choice of the 75th percentile of the entire series as the reference, including liver resections, likely shifted the balance toward short-term stays and penalized, so to speak, the TO achievement for pancreatectomy in the present study.

Coinciding with the start of the case inclusion period for this study, an article was published advocating an initial resection strategy for IPNB lesions as the first step in selecting patients who could actually benefit from liver transplantation in France, a country where this type of procedure could be commonly considered for selected patients[33]. However, two of the patients included in the present study received liver transplantation as the first option, a strategy described for some patients in another European IPNB series[11,24]. Three additional patients of the present study underwent salvage liver transplantation due to liver failure after resection surgery. The indication of liver transplantation to manage the recurrence of IPNB, as initial treatment for IPNB, or as salvage for liver failure after resection surgery are debatable issues that require further study. The difficulty lies in the impossibility of determining the presence of malignant transformation preoperatively[2].

This European study shows that the median overall survival of patients with IPNB was 5.72 years from surgery and that the 5-year overall survival was 63% (95% CI: 50–82), data that are in line with survival in other geographic regions with a higher

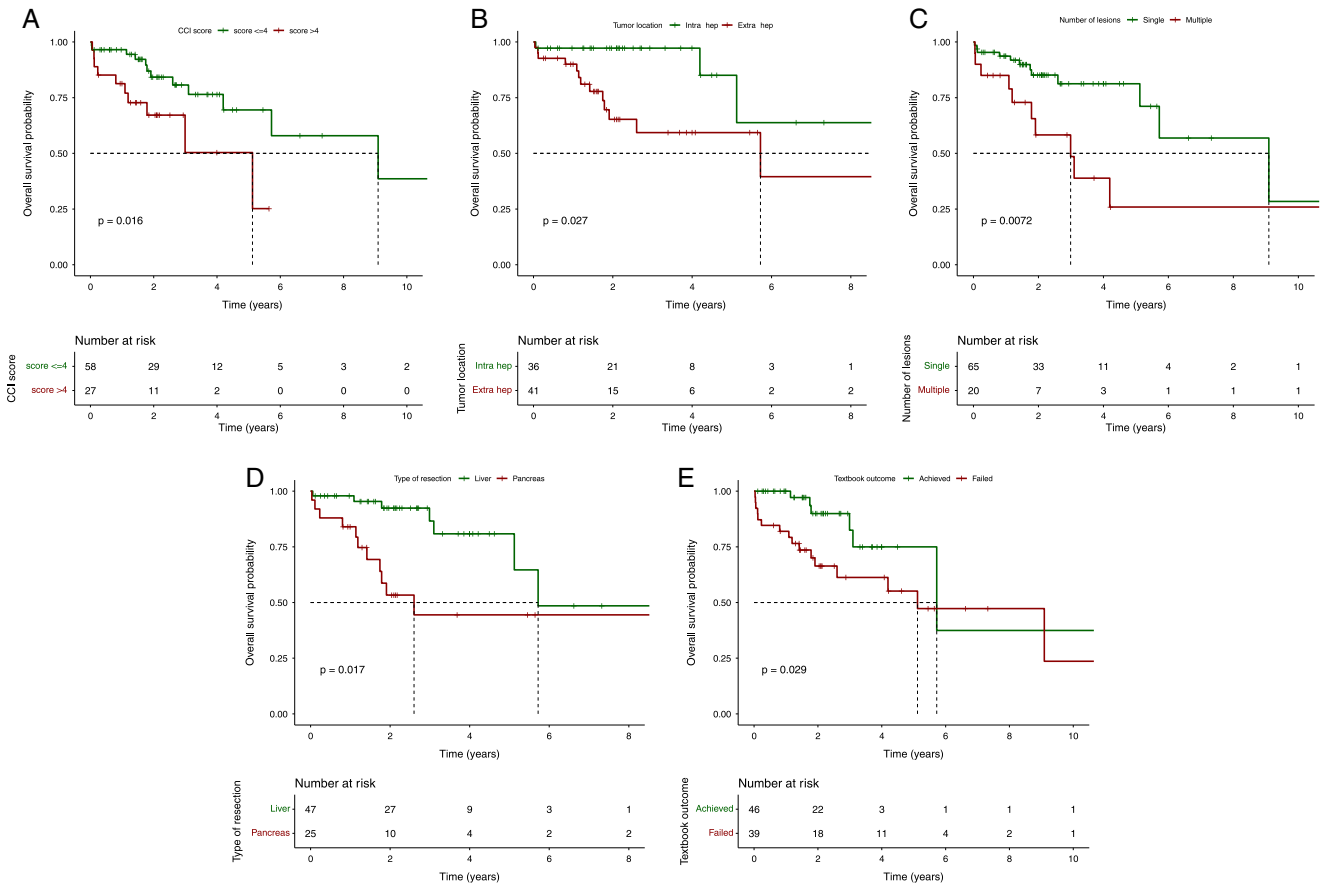

Figure 3. Overall survival of patients who underwent surgery for intraductal papillary neoplasm of the bile duct is depicted using Kaplan–Meier curves. The dotted lines indicate median survival. Log-rank analysis was performed based on: (A) Charlson Comorbidity Index (CCI score ≤ 4 versus > 4), (B) tumor location (intrahepatic versus extrahepatic), (C) tumor burden at presentation (single versus multiple tumors), (D) type of resection (liver versus pancreas), and (E) textbook outcome achievement.

incidence of IPNB. In a seminal study by Rocha *et al.*[7], the median overall survival of patients with IPNB was 5.2 years from diagnosis, and the 5-year survival was 50%. The estimated 5-year survival after IPNB resection was 65% (95% CI: 46–76) in pooled studies[29].

Comorbidity, two tumor characteristics (location, number of tumors), and the resected organ (liver or pancreas) influenced overall survival in this European study. Similarly, a study by Matsumoto *et al.*[34] showed that patients with intrahepatic IPNBs had better postoperative recurrence-free survival than patients with extrahepatic IPNBs, and multiple IPNBs had poorer survival than single IPNBs in a study from Korea[35]. In our study, patients who underwent hepatic resection achieved better overall survival than those who underwent pancreatic resection. Gender, tumor epithelial cell subtype (intestinal, pancreaticobiliary, gastric, oncocytic), and positive surgical resection margin did not influence survival in this European study. Other previous studies had found similar or opposite results. For instance, positive resection margin was associated with poorer median overall survival, while age, gender, primary tumor location, and epithelial cell subtype were not associated with survival in the study by Rocha *et al.*[7]. By contrast, no difference in overall or progression-free survival was found between patients with a positive bile duct margin and those with a negative bile duct margin in the study by Kubota *et al.*[9]. In the present study, no association was found between IPNB morphology and survival. Differences in survival according to epithelial cell subtype were reported in the study by Klöppel *et al.*[6]. Consistent with biliary tract malignancies, the finding of positive regional lymph nodes harvested by lymph node dissection was associated with poorer overall and progression-free survival[36].

This European series identified a surgical metric (not achieving TO) as an independent predictor of poor overall survival in patients with IPNB. As a novel finding, the association of failure to achieve TO seems both predictable and informative. Studies in Asia identified several tumor-specific factors associated with survival in patients with IPNB. Most studies agreed on a positive resection margin as an independent prognostic factor for poor survival[35,37–40]. Furthermore, tumor burden (multiplicity)[35], lymph node invasion[38,40], perineural invasion[39], or degree of tumor invasiveness[41] emerged as independent prognostic factors for poor survival in some of these studies.

Among the limitations, this is a retrospective study, and therefore the patients were subjected to different diagnostic and therapeutic strategies over time. BilIN was found in 24 patients (28.3%) in our series, although it was not reported in

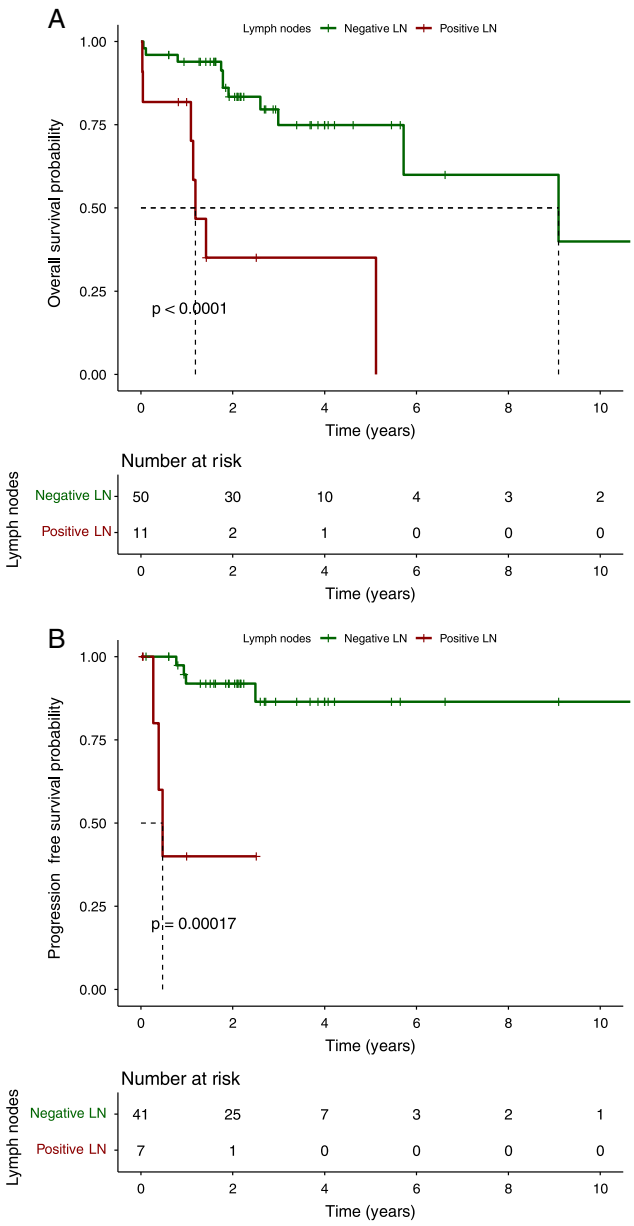

Figure 4. Overall survival (A) and progression-free survival (B) of patients who underwent lymph node dissection for intraductal papillary neoplasm of the bile duct, depicted using the Kaplan–Meier curve. The dotted lines indicate median survival (median progression-free survival was not reached in patients with negative lymph nodes).

all patients; BilIN is postulated as a precursor to invasive carcinoma of the bile ducts, but its actual incidence has not been determined[1]. Three-quarters of patients underwent lymph node dissection, and a median of six lymph nodes was obtained. Dissection rates and numbers of lymph nodes harvested were within the ranges established by recent recommendations for malignancies of biliary origin. Unfortunately, data on dissected lymph node stations were not available. Lymph node invasion was found in the resection specimens of 11 patients (12.9%) with IPNB, an apparently low proportion but[37] similar to that described in several series, more frequent in extra- than intrahepatic IPNBs[7,24,34,35]. The study protocol

Table 5

Multivariable Cox analysis of prognostic factors associated with overall survival for patients with IPNB who underwent surgical resection.

	Multivariable	
Factors	**Hazard ratio (95% CI)**	***P***
Textbook outcome		
Achieved	1 [Reference]	
Failed	4.20 (1.11–15.94)	0.03

IPNB, intraductal papillary neoplasm of the bile duct.

did not include recording the degree of atypia found in the invaded resection margin. Given the small number of cases, the anatomical diversity of the invaded margins, and the non-association of the invaded resection margin with overall survival in our series, it is tempting to speculate that the degree of atypia found in the resection margin would not have provided additional information in the present study. The detection of intraluminal mucin by the surgeon is somewhat subjective. For this reason, analyses were carried out by taking mucin found in pathology as a reference. Intraluminal mucin was found in 44% of patients in a systematic review, indicating that the presence of intraluminal mucin was of little use in differentiating IPNB from other biliary tumors[29]. Recently, IPNB lesions have been subclassified into type-1 and type-2[8,9]. Unfortunately, the recruitment period for our study dates back to 2010, making it difficult for researchers to label tumors according to this subclassification and establish any association with survival. Among the strengths, patients were treated in tertiary centers with high volume and experience in HPB surgery, and it is the largest European series of patients with IPNB published to date.

Conclusions

In conclusion, patients undergoing liver resection for IPNB were more likely to achieve a TO than those requiring a pancreatic resection. Failing to achieve TO was an independent prognostic factor of poor overall survival. A prospective registry of patients would increase knowledge and improve the management of this disease.

Ethical approval

The ethics committee of the Vall d'Hebron Hospital, Barcelona, Spain, approved the study protocol on 2 December 2021, and waived the informed consent of patients due to the retrospective nature of the study (PR[AG]469/2021).

Patient consent

Patient consent was waived due to the observational design of this study.

Sources of funding

None.

Author contribution

CRediT authorship contribution statement – J.M.R., M.S.-M., and M.L.: conception and design; M.S.-M., N.L., and M.A.: administrative support; N.L.: collection and assembly of data and manuscript writing; N.L., J.M.R., M.S.-M., M.A., and M.L.: data analysis and interpretation. All authors were involved in the provision of study materials or patients and the final approval of the manuscript.

Conflicts of interest disclosure

The authors declare none related to the topic of the article.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry.
2. Unique identifying number or registration ID: 8223.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-theregistry#home/registrationdetails/6301cd2ae0bab60023029214/.

Guarantor

José Manuel Ramia.

Provenance and peer review

Not commissioned, externally peer-reviewed

Data availability statement

Due to the multicenter nature of the study, coordinators decided that raw data would remain confidential and would not be shared.

References

[1] Ainechi S, Lee H. Updates on precancerous lesions of the biliary tract: biliary precancerous lesion. Arch Pathol Lab Med 2016;140:1285–9.
[2] Desjonqueres E, Campani C, Marra F, *et al*. Preneoplastic lesions in the liver: molecular insights and relevance for clinical practice. Liver Int 2022;42:492–506.
[3] Lendvai G, Szekerczés T, Illyés I, *et al*. Cholangiocarcinoma: classification, histopathology and molecular carcinogenesis. Pathol Oncol Res 2020;26:3–15.
[4] Aslam A, Wasnik AP, Shi J, *et al*. Intraductal papillary neoplasm of the bile duct (IPNB): CT and MRI appearance with radiology–pathology correlation. Clin Imaging 2020;66(April):10–7.
[5] IARC Publications. Digestive System Tumors WHO Classification of Tumours Series, 5th ed, Vol 1. International Agency for Research on Cancer; 2019.
[6] Klöppel G, Adsay V, Konukiewitz B, *et al*. Precancerous lesions of the biliary tree. Best Pract Res Clin Gastroenterol 2013;27:285–97.
[7] Rocha FG, Lee H, Katabi N, *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.
[8] Onoe S, Ebata T, Yokoyama Y, *et al*. A clinicopathological reappraisal of intraductal papillary neoplasm of the bile duct (IPNB): a continuous spectrum with papillary cholangiocarcinoma in 181 curatively resected cases. HPB 2021;23:1525–32.
[9] Kubota K, Jang JY, Nakanuma Y, *et al*. Clinicopathological characteristics of intraductal papillary neoplasm of the bile duct: a Japan–Korea collaborative study. J Hepatobiliary Pancreat Sci 2020;27:581–97.
[10] Tan Y, Milikowski C, Toribio Y, *et al*. Intraductal papillary neoplasm of the bile ducts: a case report and literature review. World J Gastroenterol 2015;21:12498–504.
[11] Schlitter AM, Born D, Bettstetter M, *et al*. Intraductal papillary neoplasms of the bile duct: stepwise progression to carcinoma involves common molecular pathways. Mod Pathol 2014;27:73–86.
[12] Van Roessel S, Mackay TM, Van Dieren S, *et al*. Textbook outcome: nationwide analysis of a novel quality measure in pancreatic surgery. Ann Surg 2020;271:155–62.
[13] Mehta R, Tsilimigras DI, Paredes AZ, *et al*. Dedicated cancer centers are more likely to achieve a textbook outcome following hepatopancreatic surgery. Ann Surg Oncol 2020;27:1889–97.
[14] Merath K, Chen Q, Bagante F, *et al*. Textbook outcomes among medicare patients undergoing hepatopancreatic surgery. Ann Surg 2020;271:1116–23.
[15] Mathew G, Agha R. STROCSS Group. STROCSS 2021: strengthening the reporting of cohort, cross-sectional and case–control studies in surgery. Int J Surg 2021;96(November):106165.
[16] Roffman CE, Buchanan J, Allison GT. Charlson comorbidities index. J Physiother 2016;62:171.
[17] Halls MC, Berardi G, Cipriani F, *et al*. Development and validation of a difficulty score to predict intraoperative complications during laparoscopic liver resection. Br J Surg 2018;105:1182–91.
[18] 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;240:205–13.
[19] Brooke-Smith 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;17:46–51.
[20] Rahbari NN, Garden OJ, Padbury R, *et al*. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713–24.
[21] Rahbari NN, Garden OJ, Padbury R, *et al*. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). HPB 2011;13:528–35.
[22] Bassi C, Marchegiani G, Dervenis C, *et al*. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery 2017;161:584–91.
[23] Wente MN, Bassi C, Dervenis C, *et al*. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142:761–8.
[24] Schlitter AM, Jang KT, Klöppel G, *et al*. Intraductal tubulopapillary neoplasms of the bile ducts: clinicopathologic, immunohistochemical, and molecular analysis of 20 cases. Mod Pathol 2015;28:1249–64.
[25] Zen Y, Pedica F, Patcha VR, *et al*. Mucinous cystic neoplasms of the liver: a clinicopathological study and comparison with intraductal papillary neoplasms of the bile duct. Mod Pathol 2011;24:1079–89.
[26] Campbell F, Cairns A, Duthie F, *et al*. Dataset for the histopathological reporting of carcinomas of the pancreas, ampulla of vater and common bile duct. The Royal College of Pathologists; 2017. www.rcpath.org
[27] Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
[28] Gyawali B, Eisenhauer E, Tregear M, *et al*. Progression-free survival: it is time for a new name. Lancet Oncol 2022;23:328–30.
[29] Gordon-Weeks AN, Jones K, Harriss E, *et al*. Systematic review and meta-analysis of current experience in treating IPNB clinical and pathologica l corre lates. Ann Surg 2016;263:656–63.
[30] Zen Y, Jang KT, Ahn S, *et al*. Intraductal papillary neoplasms and mucinous cystic neoplasms of the hepatobiliary system: demographic differences between Asian and Western populations, and comparison with pancreatic counterparts. Histopathology 2014;65:164–73.
[31] D'Souza MA, Isaksson B, Löhr M, *et al*. The clinicopathological spectrum and management of intraductal papillary mucinous neoplasm of the bile duct (IPMN-B). Scand J Gastroenterol 2013;48:473–9.

[32] Woodhouse B, Panesar D, Koea J. Quality performance indicators for hepato-pancreatico-biliary procedures: a systematic review. HPB (Oxford) 2021;23:1–10.
[33] Vibert E, Dokmak S, Belghiti J. Surgical strategy of biliary papillomatosis in Western countries. J Hepatobiliary Pancreat Sci 2010;17:241–5.
[34] Matsumoto T, Kubota K, Hachiya H, *et al*. Impact of tumor location on postoperative outcome of intraductal papillary neoplasm of the bile duct. World J Surg 2019;43:1313–22.
[35] Kang MJ, Jang JY, Lee KB, *et al*. Impact of macroscopic morphology, multifocality, and mucin secretion on survival outcome of intraductal papillary neoplasm of the bile duct. J Gastrointest Surg 2013;17:931–8.
[36] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Hepatobiliary Cancers, version 2; 2022. Accessed 24 August 2022. https://www.nccn.org/guidelines/recently-published-guidelines
[37] Kim WJ, Hwang S, Lee YJ, *et al*. Clinicopathological features and long-term outcomes of intraductal papillary neoplasms of the intrahepatic bile duct. J Gastrointest Surg 2016;20:1368–75.
[38] Luvira V, Pugkhem A, Bhudhisawasdi V, *et al*. Long-term outcome of surgical resection for intraductal papillary neoplasm of the bile duct. J Gastroenterol Hepatol 2017;32:527–33.
[39] Kim JR, Lee KB, Kwon W, *et al*. Comparison of the clinicopathologic characteristics of intraductal papillary neoplasm of the bile duct according to morphological and anatomical classifications. J Korean Med Sci 2018;33:e266.
[40] Uemura S, Higuchi R, Yazawa T, *et al*. Prognostic factors for surgically resected intraductal papillary neoplasm of the bile duct: a retrospective cohort study. Ann Surg Oncol 2021;28:826–34.
[41] Kim JR, Jang KT, Jang JY, *et al*. Clinicopathologic analysis of intraductal papillary neoplasm of bile duct: Korean multicenter cohort study. HPB (Oxford) 2020;22:1139–48.