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

--Manuscript Draft--

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Abstract:	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 January 1, 2010, and December 31, 2020 was gathered under the auspices of the E-AHPBA. Textbook outcome was defined as non-prolonged length of hospital stay plus absence of any Clavien-Dindo grade ≥III complication, readmission, or mortality within 90 postoperative days. Results A total of 28 centers contributed 85 patients who underwent surgery for IPNB. Median age was 66 years (55-72), 49.4% were women and 87.1% Caucasian. Open surgery was performed in 72 patients (84.7%), laparoscopic in 13 (15.3%). Textbook outcome 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 vs >4 (P=.016), intra- vs extra-hepatic tumor (P=.027), single vs multiple tumor (P=.007), those who underwent hepatic vs pancreatic resection (P=.017), or achieved vs failed textbook outcome (P=.029). Multivariable Cox regression analysis showed that not achieving textbook outcome (HR 4.20, 95% CI 1.11-15.94, P=.03) was an independent prognostic factor of poor overall survival. Conclusions Patients undergoing liver resection for IPNB were more likely to achieve a textbook outcome than those requiring a pancreatic resection. Comorbidity, tumor location and tumor multiplicity influenced overall survival. Textbook outcome was an independent prognostic factor of overall survival.

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The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories, then this should be stated.

Please state any conflicts of interest

None

Please state any sources of funding for your research

None

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

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

Research Registration Unique Identifying Number (UIN)

The World Medical Association's Declaration of Helsinki 2013 states in article 35: *'Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject'*. Editors of IJS require that all types of research studies involving human participants should be registered prospectively and failing that retrospectively. There are many places to register your research, and you can choose which is the most suitable for your needs:

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Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

CRediT authorship contribution statement

(I) Conception and design: José Manuel Ramia, Mario Serradilla-Martín, Mickaël Lesurtel.
(II) Administrative support: Mario Serradilla-Martín, Nuria Lluís, Mar Achalandabaso.
(III) Provision of study materials or patients: All authors.
(IV) Collection and assembly of data: Nuria Lluís.
(V) Data analysis and interpretation: Nuria Lluís, José Manuel Ramia, Mario Serradilla-Martín, Mar Achalandabaso, Mickaël Lesurtel.
(VI) Manuscript writing: Nuria Lluís.
(VII) Final approval of manuscript: All authors.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. Please note that providing a guarantor is compulsory.

José Manuel Ramia

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Ms. Ref. No.: IJS-D-22-01120
Title: Intraductal papillary neoplasms of the bile duct: A European retrospective multicenter observational study (EUR-IPNB Study)
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Dear Editor-in-Chief,

Thank you very much for giving us the opportunity to review our manuscript. We would like to draw your attention to **Reviewer #1's** insightful comment #16, and the major changes it has brought about in the revised version of the manuscript we are resubmitting.

A revised version of the manuscript (body, tables and figures, and supplementary material) is provided. It includes all changes resulting from the new statistical analysis, as well as responses to comments from the editor and reviewers. Given the diversity of changes, a version with all the changes made, and a final version with the changes accepted are attached.

Below is the list of our point-by-point reply and changes according to the editors and reviewer's comments.

We thank you in advance for your consideration of this manuscript and look forward to the opportunity to work with your editorial team and peer reviewers should it require further refinements prior to publication.

Sincerely,

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Managing Editor

Please can you make the following changes/checks:

1) Ensure your work is fully compliant with the STROCSS 2021 criteria www.strocssguideline.com, which should be cited within the methods section of your article and please submit a completed STROCSS checklist stating the page numbers where you completed each item (your work will be returned if this is not done).

The following sentence is included in Patients and Methods/Study Design:

> *"Planning and analysis of the study was carried out according to the STROCCS Reporting Guidelines for Cohort Studies."*

A completed STROCSS checklist is submitted.

Please also ensure your methods section states that the work has been reported in line with the STROCSS criteria and cite the paper as follows:

Mathew G and Agha R, for the STROCSS Group. STROCSS 2021: Strengthening the Reporting of cohort, cross-sectional and case-control studies in Surgery. International Journal of Surgery 2021; 96:106165.

The paper is included in References:

> *"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 2021):106165. doi: 10.1016/j.ijsu.2021.106165."

2) Please ensure you submit your work with a Research Registry UIN: e.g., from www.researchregistry.com – it can't progress without being registered – even it its retrospective research. Please ensure you also state your registration unique identifying number (UIN) in your methods section and reference it including a hyperlink to it.

A Research Registry UIN is included in Patients and Methods/Study Design, as well as a hyperlink.

3) Please go through your paper and proofread it to correct spelling, grammar and syntax errors. If you need our author support services, you can access them here: https://www.ijspg.com/services/author-support.

We have grammatically checked the text to the best of our abilities.

4) If you haven't already, please include your "highlights" which are 3-5 bullet points summarizing the novel aspects and/or learning points (maximum 85 characters, including spaces, per bullet point).

The highlights are included:

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*

5) Please add the following statement above references:

Provenance and peer review
Not commissioned, externally peer-reviewed.

The following is added above References:

> *"Provenance and peer review*
> *Not commissioned, externally peer-reviewed"*

Reviewer #1

1. In the 'introduction' section, the authors should provide the risk factors of IPNB in Asian patients other than hepatolithiasis and Clonorchiasis.

Following the reviewer's suggestion, the following has been added to Introduction:

> *"Other risk factors include primary sclerosing cholangitis, biliary malformations, and familial adenomatous polyposis/Gardner syndromes. (Klöppel 2013)"*

2. Any other kind of parasites had been recorded?

No other parasite was recorded in the patients included in the study.

3. The authors should provide the common definition and criteria for diagnosis of IPNB among the centers. Was the surgical specimen and histopathology reviewed before recruitment of the patient?

Indeed, this information was missing from the manuscript and, following the reviewer's observation, has now been included in Study Design:

> "*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. (WHO 2019) It was left to each participating center the responsibility of reviewing the pathology and all relevant data before recruiting the patient for the study."*

4. Since there are several kinds of intraductal bile duct tumor, according to the proportion of papillary - tubular component. How authors differentiate intraductal tubular and papillotubular neoplasm from IPNB?

The 2019 WHO tumor classification defined IPNB of the liver and bile ducts as "a grossly visible premalignant neoplasm with intraductal papillary or villous growth of biliary-type epithelium," which may harbor a component of invasive carcinoma. This updated WHO classification accepted biliary papilloma and papillomatosis as related terminology; however, it did not recommend the use of terms such as papillary or tubulo-papillary adenoma, among others. Since this is an evolving area, it was agreed that the investigators would select cases based on these updates.

5. The authors should provide more details of surgical margin status, according to degree of atypia on surgical margin, because there is an association between degree of atypia on surgical margin status and survival of the patients.

We recognize that it would have been useful and interesting to have this information. However, the study protocol did not include recording the degree of atypia found in the invaded resection margin. To a large extent, it was not included in the study protocol because it was felt that it would be missing in most cases. On the other hand, delving into the data collected, 15 (17.7%) of our patients had invasion of the resection margin. The invaded margin corresponded to the cystic duct or common bile duct, or to the parenchyma (Table 4). Furthermore, in our series of patients, invaded resection margin was not associated with overall survival in multivariable analysis (Supplementary Table 5). Looking back and given the small number of cases, the anatomical diversity of the margins invaded, and the lack of association with overall survival, 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. Based on this reasoning, the following comments have been added to the Discussion:

> *"The study protocol 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."*

6. I do agree that the authors categorized IPNB, according to degree of atypia, into adenoma, low grade dysplasia, high grade dysplasia, invasive carcinoma. I encourage the authors to determine the association between degree of atypia and survival of the patient, presented by survival curve. From the latest classification, the term 'carcinoma in situ' is discourage, because of its clinical ambiguity, and should be encompassed by high grade dysplasia.

We appreciate the comment as it prompts to add a sentence that was missing in Results/Survival analysis:

"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."

7. Detection of intraluminal mucin, by the surgeon, is somewhat subjective. The author should clarify the definition of intraluminal mucin detection. The presence of mucin on histopathological examination is more important.

We totally agree with the reviewer. Therefore, association analysis with textbook outcome, overall survival and progression-free survival were performed taking mucin found in pathology as a reference. For comparison purposes only, the *kappa* coefficient showed that the detection of mucin by the surgeon showed a substantial strength of agreement with that detected by pathology. The following sentence has been added to Discussion:

"Detection of intraluminal mucin by the surgeon is somewhat subjective. For this reason, the analyses were carried out taking mucin found in pathology as reference."

8. Were the patients, who had postoperative dead (died within 30 [or 90] days after the operation), censored from survival analysis?

As stated in Results/Analysis, overall survival and progression-free survival were defined from the date of surgery. Therefore, patients who died during the first months due to postoperative-related mortality were not censored.

9. Any record about the station (location) of the lymph node dissected?

The question posed by the reviewer would have been very interesting to answer, but unfortunately data on dissected lymph node stations were not available. We were only able to ascertain that about three quarters of patients underwent lymph node dissection and that 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. Consequently, the following comments have been added to the Discussion:

"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. (NCCN 2022) Unfortunately, data on dissected lymph node stations were not available."

10. The authors should discuss about why choosing TO as the outcome of interest.

In addition to the traditional outcomes provided in the Results section, the textbook outcome is a composite metric that includes the above in a single figure and thus simplifies comparisons between groups and facilitates association analysis. To address the reviewer's comment, the following has been added to Discussion:

"The TO is a composite metric that simplifies comparison between groups and facilitates analysis of association."

11. Any record about the morphology of the IPNB, and its association with patient survival?

In response to comment #6, it was stated that no association was found between degree of atypia, or type of epithelial cell, and survival. Based on this, the following sentence has been added to the Discussion:

"In the present study, no association was found between IPNB morphology and survival."

12. The term "Disease-free survival" should be used, instead of "progression-free survival", to describe the interval between the date of surgery and the date of recurrence diagnosis.

We agree with the reviewer that disease-free survival is common terminology. In the last two decades, however, progression-free survival has been widely used to refer to outcomes in oncology clinical trials. On the other hand, the most recent literature suggests changing progression-free survival to progression-free interval. At the moment, and pending the evolution of the term, we have opted for progression-free survival in this manuscript. The following reference has been added to Patients and Methods/Analysis:

"Gyawali B, Eisenhauer E, Tregear M, Booth CM. Progression-free survival: it is time for a new name. Lancet Oncol. 2022;23(3):328-330. doi:10.1016/S1470-2045(22)00015-8."

13. Why the male predominated in this series? The authors should discuss about this issue.

In the present series, the proportion of males and females was around 50%, without significant gender differences. Some series from Asia show predominance of males, although without significant differences (Onoe 2014) The following sentence has been added to Discussion:

"There were no significant gender differences."

14. How the authors categorized the location of the IPNB in case of multiple lesions?

According to the WHO tumor classification, some IPNB appear as multiple contiguous lesions, while others are isolated lesions and multiple lesions may develop. In either case, the pathologist was ultimately responsible for labeling the lesion as intrahepatic or extrahepatic, the latter being above or below the cystic duct. The following sentence has been added to Discussion:

"The pathologist was ultimately responsible for labelling the lesion as intrahepatic or extrahepatic, the latter being above or below the cystic duct."

15. Was does 'pancreatic involvement' mean? Was it pancreas invasion or simultaneous IPNB and IPMN-P? Please clarify.

All tumors were IPNB. The need for pancreatic resection is now explained in Discussion:

> *"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."*

16. Please provide the indication for total pancreatectomy in two patients.

The authors appreciate the reviewer's insightful comment upon noticing a surgical procedure that we had reported without paying due attention to. As a consequence of this observation, the following major changes have been made:

a) Searching PubMed with the terms "intraductal papillary neoplasm of the bile duct" and "total pancreatectomy" found one citation (Scand J Gastroenterol. 2013 Apr;48[4]:473-9). It is interesting to note that the first author of this article is also a co-author of the present study. The article described seven patients with intraductal papillary mucinous neoplasm of the bile duct (IPMN-B). One patient had a tumor that invaded the entire extrahepatic biliary tract, including the left hepatic duct. The patient underwent left hepatectomy and total pancreatectomy. The decision to perform total pancreatectomy was made after intraoperative frozen sample of the pancreatic resection margin revealed moderate dysplasia, and after taking into account the extent of the resection and the high risk of pancreatic fistula from the pancreatic anastomosis.

b) Similar circumstances occurred in one of our patients. He was an elderly male, with IPNB of intrapancreatic bile duct, who underwent pancreaticoduodenectomy. Intraoperative frozen examination showed invasion of the pancreatic resection margin. In addition, the patient had multiple enlarged regional lymph nodes, and atrophy of the body and tail of the pancreas. Indeed, lymph node dissection harvested 25 lymph nodes, and 11 were positive on definitive pathologic examination. The decision to perform total pancreatectomy was made after taking into account the extent of the resection and the high risk of pancreatic fistula.

c) Most importantly, the reviewer's question prompted an in-depth re-evaluation of the second patient undergoing total pancreatectomy. After a thorough review, the participating center confirmed that it was an intraductal papillary mucinous neoplasm of the pancreas. Therefore, this patient has been removed from the present study and, consequently, the co-researcher who contributed only this case is no longer a co-author.

d) Consequently, the statistical analysis of the entire series (i.e., descriptive, association, survival) has been carried out again. Certainly, it has been a huge but unavoidable job. Above all, maintaining the integrity of the data reported and the meaning of the results achieved is imperative.

e) A revised version of the manuscript (body, tables and figures, and supplementary material) is provided. It includes all changes resulting from the new statistical analysis, as well as responses to comments from the editor and reviewers. Given the diversity of changes, a version with all the changes made, and a final version with the changes accepted are attached.

f) The removed patient was a male, of non-Caucasian ethnicity, who presented early recurrence and died a year after surgery. These data could explain the changes detected in the new version of the manuscript. As expected in a Western series of patients, there were few non-Caucasian patients. The withdrawal of one patient led to the disappearance of ethnicity as a prognostic factor for survival. Similarly, comorbidity and tumor multiplicity do not appear as prognostic factors for survival. However, comorbidity, tumor location, tumor multiplicity, type of resection, and textbook outcome continue to have an impact on overall survival, as reflected in the Kaplan-Meier curves provided in the new version.

In addition to the aforementioned major changes, the following has been added to Discussion:

> *"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 twenty-five lymph nodes, eleven 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. (D'Souza 2013)"*

17. Was there any association between lymph node involvement and survival of the patients?

Lymph node involvement was detected in 11 of 61 patients who underwent lymph node dissection. Overall and progression-free survival curves comparing both cohorts are now presented in Fig 4. The following has been added to Results/Survival analysis:

> *"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)."*

and to Discussion:

> *"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. (NCCN 2022)"*

18. Please discuss about the suspected cause of IPNB in Europe.

The following has been added to Discussion:

"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 (Rocha 2012). Both characteristics seem to stand the test of time in recent publications (Desjonquères 2022). On the other hand, the oncocytic subtype seems to be more frequent in Western populations (Schlitter 2014), although it was a minority in our series. Indeed, IPNBs identified in the West are more likely to be extrahepatic and invasive (Gordon-Weeks 2015). While in Asia many cases are associated with flukes and stones, most IPNBs in Western countries are sporadic (Klöppel 2013) 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 (Zen 2014). 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."

19. Please discuss why pancreas resection was associated with decreased odds of TO achievement.

We appreciate the reviewer's comment. The following paragraph has been added to Discussion:

"High morbidity associated with pancreato-intestinal anastomosis (fistula, hemorrhage, infection) could explain the worse TO of pancreatic resection compared to hepatic resection. (Woodhouse 2021) 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, (van Roessel 2020) 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 towards short-term stays and penalized, so to speak, the TO achievement for pancreatectomy in the present study."

20. Please provide the definition of 'Local communication with adjacent bile duct'

Biliary cystic tumors are not connected to the bile ducts. Consequently, biliary cystic tumors with communication to the bile ducts are considered as cystic variants of IPNB. Bile duct communication in IPNB is evidenced by the presence of intraepithelial neoplasms within adjacent bile ducts, or the presence of peribiliary glands in the cyst wall. The following has been added to Patients and Methods/Pathology:

"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. (Zen 2011)"

Reviewer #3

What is the rationale of using the term "textbook outcome"?

Obviously, we had overlooked that the concept was not yet clearly established or common domain. Thanks to reviewer feedback, we have added the following to Introduction:

> *"Recently, the term textbook outcome 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. (van Roessel 2020, Mehta 2020, Merath 2020)"*

The authors noted that "Intraluminal mucin was seen in 18 patients (20.9%)". Does this mean that they included ITPN-B (Intraductal tubulopapillary neoplasms of the biliary tract) cases as well? Considering the different underlying pathogenetic mechanisms and significantly different prognosis between these two entities (IPNB vs. ITPN), this aspect should be clarified. And if possible, the prognosis of these subgroups should be compared.

We thank the reviewer for the opportunity to emphasize the relevance of intraluminal mucin. IPNB may present with mucus hypersecretion secretion, more commonly in Asian than in Western patients. (WHO 2019) In fact, intraluminal mucin was found in 21.2% of our IPNB patients at surgery, and in 31.8% of IPNB tumors at pathology. Furthermore, 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. (Gordon-Weeks 2016) On the other hand, we found no difference in survival based on the presence or absence of intraluminal mucin in our patients. Patients with intraductal tubulopapillary neoplasms were not included in this study. We have added the following to Results/Survival analysis:

> *"There was no difference in overall survival according to the presence of mucin, …."*

and to Discussion:

> *"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. (Gordon Weeks 2016)"*

Was the size and/or type of invasion a significant prognostic factor? How many cases had invasion? And were all the cases adenocarcinoma? How did the authors evaluate such aspects?

Analysis based on stromal, vascular, lymphatic, or perineural invasion was not feasible as pathology data were missing for a substantial number of patients (see Table 4). However, we have added survival analyzes according to the status of lymph nodes harvested at lymph node dissection. Lymph node involvement was detected in 11 of 61 patients who underwent lymph node dissection. Overall and progression-free survival

curves comparing both cohorts are now presented in Fig 4. The following has been added to Results/Survival analysis:

> *"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)."*

and to Discussion:

> *"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. (NCCN 2022)"*

How did the authors distinguish between IPNB and high-grade BilIN?

Biliary intraepithelial neoplasia (BilIN) is one of the suggested pathways of biliary carcinogenesis. According to the WHO tumor classification, IPNB is "a grossly visible premalignant neoplasm with intraductal papillary or villous growth of biliary-type epithelium" that may harbor an associated invasive carcinoma. (WHO 2019) In fact, areas of BilIN adjacent to IPNB itself may be present. (Zen 2014) In any case, the distinction between IPNB and BilIN is feasible.

The negative effect of the pancreatic resection on survival should be further discussed.

We appreciate the reviewer's comment. In fact, pancreatectomy negatively affected textbook outcome. The following paragraph has been added to Discussion:

> *"High morbidity associated with pancreato-intestinal anastomosis (fistula, hemorrhage, infection) could explain the worse TO of pancreatic resection compared to hepatic resection. (Woodhouse 2021) Pancreatic duct diameter and pancreatic parenchyma consistency, 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, (van Roessel 2020) 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 towards short-term stays and penalized, so to speak, the TO achievement for pancreatectomy in the present study."*

Reviewer #4

This paper is dealing with IPNB experienced in Europe. The data are new in this area, and are comparable with data of Asian countries. The differences in the subtype and location of IPNB from those of Asian countries are reasonable. I think this paper send important messages to this field.

We appreciate the reviewer's comment and support.

Editor-in-Chief

This is a well-written article on a relatively large cohort of patients with intraductal papillary neoplasms of the bile duct coming from multicenter in Europe. I encourage the authors to respond to all the points raised by the Reviewers and resubmit the article to our Journal.

We appreciate the editor's feedback and the opportunity to revise our manuscript.

Potential reviewer

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Managing Editor

Please can you make the following changes/checks:

1) Ensure your work is fully compliant with the STROCSS 2021 criteria www.strocssguideline.com, which should be cited within the methods section of your article and please submit a completed STROCSS checklist stating the page numbers where you completed each item (your work will be returned if this is not done).

The following sentence is included in Patients and Methods/Study Design:

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A completed STROCSS checklist is submitted.

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The paper is included in References:

> *"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 2021):106165. doi: 10.1016/j.ijsu.2021.106165."

2) Please ensure you submit your work with a Research Registry UIN: e.g., from www.researchregistry.com – it can't progress without being registered – even it its retrospective research. Please ensure you also state your registration unique identifying number (UIN) in your methods section and reference it including a hyperlink to it.

A Research Registry UIN is included in Patients and Methods/Study Design, as well as a hyperlink.

3) Please go through your paper and proofread it to correct spelling, grammar and syntax errors. If you need our author support services, you can access them here: https://www.ijspg.com/services/author-support.

We have grammatically checked the text to the best of our abilities.

4) If you haven't already, please include your "highlights" which are 3-5 bullet points summarizing the novel aspects and/or learning points (maximum 85 characters, including spaces, per bullet point).

The highlights are included:

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*

5) Please add the following statement above references:

Provenance and peer review
Not commissioned, externally peer-reviewed.

The following is added above References:

> *"Provenance and peer review*
> *Not commissioned, externally peer-reviewed"*

Reviewer #1

1. In the 'introduction' section, the authors should provide the risk factors of IPNB in Asian patients other than hepatolithiasis and Clonorchiasis.

Following the reviewer's suggestion, the following has been added to Introduction:

> *"Other risk factors include primary sclerosing cholangitis, biliary malformations, and familial adenomatous polyposis/Gardner syndromes. (Klöppel 2013)"*

2. Any other kind of parasites had been recorded?

No other parasite was recorded in the patients included in the study.

3. The authors should provide the common definition and criteria for diagnosis of IPNB among the centers. Was the surgical specimen and histopathology reviewed before recruitment of the patient?

Indeed, this information was missing from the manuscript and, following the reviewer's observation, has now been included in Study Design:

> "*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. (WHO 2019) It was left to each participating center the responsibility of reviewing the pathology and all relevant data before recruiting the patient for the study."*

4. Since there are several kinds of intraductal bile duct tumor, according to the proportion of papillary - tubular component. How authors differentiate intraductal tubular and papillotubular neoplasm from IPNB?

The 2019 WHO tumor classification defined IPNB of the liver and bile ducts as "a grossly visible premalignant neoplasm with intraductal papillary or villous growth of biliary-type epithelium," which may harbor a component of invasive carcinoma. This updated WHO classification accepted biliary papilloma and papillomatosis as related terminology; however, it did not recommend the use of terms such as papillary or tubulo-papillary adenoma, among others. Since this is an evolving area, it was agreed that the investigators would select cases based on these updates.

5. The authors should provide more details of surgical margin status, according to degree of atypia on surgical margin, because there is an association between degree of atypia on surgical margin status and survival of the patients.

We recognize that it would have been useful and interesting to have this information. However, the study protocol did not include recording the degree of atypia found in the invaded resection margin. To a large extent, it was not included in the study protocol because it was felt that it would be missing in most cases. On the other hand, delving into the data collected, 15 (17.7%) of our patients had invasion of the resection margin. The invaded margin corresponded to the cystic duct or common bile duct, or to the parenchyma (Table 4). Furthermore, in our series of patients, invaded resection margin was not associated with overall survival in multivariable analysis (Supplementary Table 5). Looking back and given the small number of cases, the anatomical diversity of the margins invaded, and the lack of association with overall survival, 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. Based on this reasoning, the following comments have been added to the Discussion:

> *"The study protocol 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."*

6. I do agree that the authors categorized IPNB, according to degree of atypia, into adenoma, low grade dysplasia, high grade dysplasia, invasive carcinoma. I encourage the authors to determine the association between degree of atypia and survival of the patient, presented by survival curve. From the latest classification, the term 'carcinoma in situ' is discourage, because of its clinical ambiguity, and should be encompassed by high grade dysplasia.

We appreciate the comment as it prompts to add a sentence that was missing in Results/Survival analysis:

"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."

7. Detection of intraluminal mucin, by the surgeon, is somewhat subjective. The author should clarify the definition of intraluminal mucin detection. The presence of mucin on histopathological examination is more important.

We totally agree with the reviewer. Therefore, association analysis with textbook outcome, overall survival and progression-free survival were performed taking mucin found in pathology as a reference. For comparison purposes only, the *kappa* coefficient showed that the detection of mucin by the surgeon showed a substantial strength of agreement with that detected by pathology. The following sentence has been added to Discussion:

"Detection of intraluminal mucin by the surgeon is somewhat subjective. For this reason, the analyses were carried out taking mucin found in pathology as reference."

8. Were the patients, who had postoperative dead (died within 30 [or 90] days after the operation), censored from survival analysis?

As stated in Results/Analysis, overall survival and progression-free survival were defined from the date of surgery. Therefore, patients who died during the first months due to postoperative-related mortality were not censored.

9. Any record about the station (location) of the lymph node dissected?

The question posed by the reviewer would have been very interesting to answer, but unfortunately data on dissected lymph node stations were not available. We were only able to ascertain that about three quarters of patients underwent lymph node dissection and that 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. Consequently, the following comments have been added to the Discussion:

"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. (NCCN 2022) Unfortunately, data on dissected lymph node stations were not available."

10. The authors should discuss about why choosing TO as the outcome of interest.

In addition to the traditional outcomes provided in the Results section, the textbook outcome is a composite metric that includes the above in a single figure and thus simplifies comparisons between groups and facilitates association analysis. To address the reviewer's comment, the following has been added to Discussion:

"The TO is a composite metric that simplifies comparison between groups and facilitates analysis of association."

11. Any record about the morphology of the IPNB, and its association with patient survival?

In response to comment #6, it was stated that no association was found between degree of atypia, or type of epithelial cell, and survival. Based on this, the following sentence has been added to the Discussion:

"In the present study, no association was found between IPNB morphology and survival."

12. The term "Disease-free survival" should be used, instead of "progression-free survival", to describe the interval between the date of surgery and the date of recurrence diagnosis.

We agree with the reviewer that disease-free survival is common terminology. In the last two decades, however, progression-free survival has been widely used to refer to outcomes in oncology clinical trials. On the other hand, the most recent literature suggests changing progression-free survival to progression-free interval. At the moment, and pending the evolution of the term, we have opted for progression-free survival in this manuscript. The following reference has been added to Patients and Methods/Analysis:

"Gyawali B, Eisenhauer E, Tregear M, Booth CM. Progression-free survival: it is time for a new name. Lancet Oncol. 2022;23(3):328-330. doi:10.1016/S1470-2045(22)00015-8."

13. Why the male predominated in this series? The authors should discuss about this issue.

In the present series, the proportion of males and females was around 50%, without significant gender differences. Some series from Asia show predominance of males, although without significant differences (Onoe 2014) The following sentence has been added to Discussion:

"There were no significant gender differences."

14. How the authors categorized the location of the IPNB in case of multiple lesions?

According to the WHO tumor classification, some IPNB appear as multiple contiguous lesions, while others are isolated lesions and multiple lesions may develop. In either case, the pathologist was ultimately responsible for labeling the lesion as intrahepatic or extrahepatic, the latter being above or below the cystic duct. The following sentence has been added to Discussion:

"The pathologist was ultimately responsible for labelling the lesion as intrahepatic or extrahepatic, the latter being above or below the cystic duct."

15. Was does 'pancreatic involvement' mean? Was it pancreas invasion or simultaneous IPNB and IPMN-P? Please clarify.

All tumors were IPNB. The need for pancreatic resection is now explained in Discussion:

> *"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."*

16. Please provide the indication for total pancreatectomy in two patients.

The authors appreciate the reviewer's insightful comment upon noticing a surgical procedure that we had reported without paying due attention to. As a consequence of this observation, the following major changes have been made:

a) Searching PubMed with the terms "intraductal papillary neoplasm of the bile duct" and "total pancreatectomy" found one citation (Scand J Gastroenterol. 2013 Apr;48[4]:473-9). It is interesting to note that the first author of this article is also a co-author of the present study. The article described seven patients with intraductal papillary mucinous neoplasm of the bile duct (IPMN-B). One patient had a tumor that invaded the entire extrahepatic biliary tract, including the left hepatic duct. The patient underwent left hepatectomy and total pancreatectomy. The decision to perform total pancreatectomy was made after intraoperative frozen sample of the pancreatic resection margin revealed moderate dysplasia, and after taking into account the extent of the resection and the high risk of pancreatic fistula from the pancreatic anastomosis.

b) Similar circumstances occurred in one of our patients. He was an elderly male, with IPNB of intrapancreatic bile duct, who underwent pancreaticoduodenectomy. Intraoperative frozen examination showed invasion of the pancreatic resection margin. In addition, the patient had multiple enlarged regional lymph nodes, and atrophy of the body and tail of the pancreas. Indeed, lymph node dissection harvested 25 lymph nodes, and 11 were positive on definitive pathologic examination. The decision to perform total pancreatectomy was made after taking into account the extent of the resection and the high risk of pancreatic fistula.

c) Most importantly, the reviewer's question prompted an in-depth re-evaluation of the second patient undergoing total pancreatectomy. After a thorough review, the participating center confirmed that it was an intraductal papillary mucinous neoplasm of the pancreas. Therefore, this patient has been removed from the present study and, consequently, the co-researcher who contributed only this case is no longer a co-author.

d) Consequently, the statistical analysis of the entire series (i.e., descriptive, association, survival) has been carried out again. Certainly, it has been a huge but unavoidable job. Above all, maintaining the integrity of the data reported and the meaning of the results achieved is imperative.

e) A revised version of the manuscript (body, tables and figures, and supplementary material) is provided. It includes all changes resulting from the new statistical analysis, as well as responses to comments from the editor and reviewers. Given the diversity of changes, a version with all the changes made, and a final version with the changes accepted are attached.

f) The removed patient was a male, of non-Caucasian ethnicity, who presented early recurrence and died a year after surgery. These data could explain the changes detected in the new version of the manuscript. As expected in a Western series of patients, there were few non-Caucasian patients. The withdrawal of one patient led to the disappearance of ethnicity as a prognostic factor for survival. Similarly, comorbidity and tumor multiplicity do not appear as prognostic factors for survival. However, comorbidity, tumor location, tumor multiplicity, type of resection, and textbook outcome continue to have an impact on overall survival, as reflected in the Kaplan-Meier curves provided in the new version.

In addition to the aforementioned major changes, the following has been added to Discussion:

> *"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 twenty-five lymph nodes, eleven 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. (D'Souza 2013)"*

17. Was there any association between lymph node involvement and survival of the patients?

Lymph node involvement was detected in 11 of 61 patients who underwent lymph node dissection. Overall and progression-free survival curves comparing both cohorts are now presented in Fig 4. The following has been added to Results/Survival analysis:

> *"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)."*

and to Discussion:

> *"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. (NCCN 2022)"*

18. Please discuss about the suspected cause of IPNB in Europe.

The following has been added to Discussion:

"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 (Rocha 2012). Both characteristics seem to stand the test of time in recent publications (Desjonquères 2022). On the other hand, the oncocytic subtype seems to be more frequent in Western populations (Schlitter 2014), although it was a minority in our series. Indeed, IPNBs identified in the West are more likely to be extrahepatic and invasive (Gordon-Weeks 2015). While in Asia many cases are associated with flukes and stones, most IPNBs in Western countries are sporadic (Klöppel 2013) 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 (Zen 2014). 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."

19. Please discuss why pancreas resection was associated with decreased odds of TO achievement.

We appreciate the reviewer's comment. The following paragraph has been added to Discussion:

"High morbidity associated with pancreato-intestinal anastomosis (fistula, hemorrhage, infection) could explain the worse TO of pancreatic resection compared to hepatic resection. (Woodhouse 2021) 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, (van Roessel 2020) 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 towards short-term stays and penalized, so to speak, the TO achievement for pancreatectomy in the present study."

20. Please provide the definition of 'Local communication with adjacent bile duct'

Biliary cystic tumors are not connected to the bile ducts. Consequently, biliary cystic tumors with communication to the bile ducts are considered as cystic variants of IPNB. Bile duct communication in IPNB is evidenced by the presence of intraepithelial neoplasms within adjacent bile ducts, or the presence of peribiliary glands in the cyst wall. The following has been added to Patients and Methods/Pathology:

"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. (Zen 2011)"

Reviewer #3

What is the rationale of using the term "textbook outcome"?

Obviously, we had overlooked that the concept was not yet clearly established or common domain. Thanks to reviewer feedback, we have added the following to Introduction:

> *"Recently, the term textbook outcome 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. (van Roessel 2020, Mehta 2020, Merath 2020)"*

The authors noted that "Intraluminal mucin was seen in 18 patients (20.9%)". Does this mean that they included ITPN-B (Intraductal tubulopapillary neoplasms of the biliary tract) cases as well? Considering the different underlying pathogenetic mechanisms and significantly different prognosis between these two entities (IPNB vs. ITPN), this aspect should be clarified. And if possible, the prognosis of these subgroups should be compared.

We thank the reviewer for the opportunity to emphasize the relevance of intraluminal mucin. IPNB may present with mucus hypersecretion secretion, more commonly in Asian than in Western patients. (WHO 2019) In fact, intraluminal mucin was found in 21.2% of our IPNB patients at surgery, and in 31.8% of IPNB tumors at pathology. Furthermore, 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. (Gordon-Weeks 2016) On the other hand, we found no difference in survival based on the presence or absence of intraluminal mucin in our patients. Patients with intraductal tubulopapillary neoplasms were not included in this study. We have added the following to Results/Survival analysis:

> *"There was no difference in overall survival according to the presence of mucin, …."*

and to Discussion:

> *"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. (Gordon Weeks 2016)"*

Was the size and/or type of invasion a significant prognostic factor? How many cases had invasion? And were all the cases adenocarcinoma? How did the authors evaluate such aspects?

Analysis based on stromal, vascular, lymphatic, or perineural invasion was not feasible as pathology data were missing for a substantial number of patients (see Table 4). However, we have added survival analyzes according to the status of lymph nodes harvested at lymph node dissection. Lymph node involvement was detected in 11 of 61 patients who underwent lymph node dissection. Overall and progression-free survival

curves comparing both cohorts are now presented in Fig 4. The following has been added to Results/Survival analysis:

> *"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)."*

and to Discussion:

> *"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. (NCCN 2022)"*

How did the authors distinguish between IPNB and high-grade BilIN?

Biliary intraepithelial neoplasia (BilIN) is one of the suggested pathways of biliary carcinogenesis. According to the WHO tumor classification, IPNB is "a grossly visible premalignant neoplasm with intraductal papillary or villous growth of biliary-type epithelium" that may harbor an associated invasive carcinoma. (WHO 2019) In fact, areas of BilIN adjacent to IPNB itself may be present. (Zen 2014) In any case, the distinction between IPNB and BilIN is feasible.

The negative effect of the pancreatic resection on survival should be further discussed.

We appreciate the reviewer's comment. In fact, pancreatectomy negatively affected textbook outcome. The following paragraph has been added to Discussion:

> *"High morbidity associated with pancreato-intestinal anastomosis (fistula, hemorrhage, infection) could explain the worse TO of pancreatic resection compared to hepatic resection. (Woodhouse 2021) Pancreatic duct diameter and pancreatic parenchyma consistency, 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, (van Roessel 2020) 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 towards short-term stays and penalized, so to speak, the TO achievement for pancreatectomy in the present study."*

Reviewer #4

This paper is dealing with IPNB experienced in Europe. The data are new in this area, and are comparable with data of Asian countries. The differences in the subtype and location of IPNB from those of Asian countries are reasonable. I think this paper send important messages to this field.

We appreciate the reviewer's comment and support.

Editor-in-Chief

This is a well-written article on a relatively large cohort of patients with intraductal papillary neoplasms of the bile duct coming from multicenter in Europe. I encourage the authors to respond to all the points raised by the Reviewers and resubmit the article to our Journal.

We appreciate the editor's feedback and the opportunity to revise our manuscript.

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

TITLE PAGE

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

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Running head:

European multicenter study on IPNB

ABSTRACT

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 January 1, 2010, and December 31, 2020 was gathered under the auspices of the E-AHPBA. Textbook outcome was defined as non-prolonged length of hospital stay plus absence of any Clavien-Dindo grade ≥III complication, readmission, or mortality within 90 postoperative days.

Results: A total of 28 centers contributed 85 patients who underwent surgery for IPNB. Median age was 66 years (55-72), 49.4% were women and 87.1% Caucasian. Open surgery was performed in 72 patients (84.7%), laparoscopic in 13 (15.3%). Textbook outcome 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 vs >4 (*P*=.016), intra- vs extra-hepatic tumor (*P*=.027), single vs multiple tumor (*P*=.007), those who underwent hepatic vs pancreatic resection (*P*=.017), or achieved vs failed textbook outcome (*P*=.029). Multivariable Cox regression analysis showed that not achieving textbook outcome (HR 4.20, 95% CI 1.11-15.94, *P*=.03) was an independent prognostic factor of poor overall survival.

Conclusions: Patients undergoing liver resection for IPNB were more likely to achieve a textbook outcome than those requiring a pancreatic resection. Comorbidity, tumor location and tumor multiplicity influenced overall survival. Textbook outcome was an independent prognostic factor of overall survival.

Keywords

Bile duct neoplasms, intraductal precursor lesion, surgical resection, textbook outcome, pancreas

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

Abbreviations

ASA, American Society of Anesthesiology

BilIN, biliary intra-epithelial neoplasia

CCI, Charlson comorbidity index

CT, computed tomography

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

ECOG, Eastern Cooperative Oncology Group

ERCP, endoscopic retrograde cholangio-pancreatography

EUS, endoscopic ultrasonography

HPB, hepato-pancreato-biliary

ICU, intensive care unit

IPNB, intraductal papillary neoplasm of the bile duct

IQR, inter-quartile range

MRI, magnetic resonance imaging

TO, textbook outcome

US, ultrasonography

1. 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 intra- and/or extra-hepatic 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- and high-grade, the latter being more frequent.[2] Depending on the type of epithelial cell, it is sub-classified 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 3 out of 4 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 <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 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.

2. PATIENTS AND METHODS

2.1.Study Design

This is an observational retrospective study of patients with IPNB lesions undergoing elective HPB surgery between January 1, 2010, and December 31, 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 December 2, 2021, and waived the informed consent of patients due to the retrospective nature of the study (PR[AG]469/2021). The study is registered in 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.[15] 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 was carried out according to the STROCCS Reporting Guidelines for Cohort Studies.[16]

2.2.Demographics, baseline characteristics, and diagnosis

In addition to demographic data and past surgical history, body mass index, ASA score, ECOG performance status, Charlson comorbidity index (CCI),[17] biliary symptoms,

serum bilirubin and CA-19.9 level, and presence of hepatolithiasis or clonorchis infestation were recorded. The contribution of preoperative imaging tests (CT, MRI, transabdominal US, ERCP, EUS, endoscopic cholangioscopy, percutaneous transhepatic cholangiography) used to identify IPNB lesions was assessed.

2.3.Intraoperative events and surgical procedures

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.[18] 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 pancreatectomy was performed.

2.4.Postoperative course

Length of ICU and hospital stay, and 90-day morbidity and mortality according to the Clavien-Dindo classification were recorded.[19] Bile leak,[20] post-hepatectomy liver failure,[21] postoperative hemorrhage,[22] pancreatic fistula,[23] delayed gastric emptying,[24] according to ISGLS or ISGPS, and other major medical complications were identified. Any additional procedures (radiological, endoscopic, or surgical) performed during index hospitalization, episodes of ICU readmission, hospital readmission, or reintervention during the first 90 days were recorded.

2.5.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 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.[25] The epithelial cells were classified as gastric, oncocytic, pancreatobiliary, or intestinal.[8,11] Additional features included 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.[26] Involvement of the resection margin of the cystic duct, common bile duct and parenchyma was examined.[27]

2.6.Textbook outcomes

The TO was defined based on the absence of all of the following: prolonged length of hospital stay (a length of hospital stay ≥75th percentile of the total cohort), 90-day Clavien-Dindo grade ≥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.

2.7.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.

2.8.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, US) hosted at Asociación Española de Gastroenterología (AEG; www.redcap.aegastro.es).[28]

2.9.Analysis

Descriptive statistics were used for demographic and baseline characteristics of patients. Quantitative variables are reported as median and interquartile range (IQR), and categorical variables as absolute and relative frequencies. Differences between groups of patients were compared using the Chi-square test or Fisher´s exact test for categorical data, the T-test for parametric quantitative data, and the Mann-Whitney U test for quantitative non-parametric data. Cohen's *kappa* coefficient was used to describe and measure inter-observer 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 date of surgery and date of death or last follow-up. Progression-free survival was defined by the interval between date of surgery and date of recurrence diagnosis, or last follow-up or death in patients without recurrence.[29] 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 .10 on univariable analysis were entered into a multivariable model. *P* values of less than .05 were considered statistically significant. All analyses were performed using RStudio, version 1.2.5001 (Integrated Development for R. RStudio, Inc., Boston, MA, USA).

3. RESULTS

3.1.Demographic and baseline characteristics

A total of 28 centers contributed 85 patients who underwent surgery for IPNB between January 1, 2010 and December 31, 2020, with a median (IQR) of 2 (1 – 4) patients per center (**Supplementary Table 1**). Demographics and baseline characteristics are presented in **Table 1**. 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 ECOG performance status 0 (57.6%). Patients had a median Charlson comorbidity index score of 4 (2 – 5) and an estimated median 10-year survival of 53% (21 – 77). One third of patients (35.3%) had 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.

3.2.Preoperative work-up and management

A representative MRI image of an IPNB is shown in **Supplementary Figure 1a**. Preoperative imaging tests, their diagnostic performance, and imaging findings are summarized in **Supplementary Table 2**. As an example, 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 a transhepatic access in five.

3.3.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 units. Liver resection was performed in 49 patients (57.6%). 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**.

3.4.Postoperative course

After surgery, 53 patients (62.4%) spent two 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 ≥III complication occurred in 32.9% of patients, mortality was 7.1%, 17 patients (20.0%) were readmitted to the hospital for seven 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%).

3.5.Pathology report

A representative photomicrograph of an IPNB is shown in **Supplementary Figure 1b**. 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**). 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%), 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 were harvested from 61 patients (71.8%). In 11 of these patients, a median of three (2 – 4) involved lymph nodes per patient were identified.

3.6.Textbook outcomes

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 was 32.0% after pancreas resection (**Figure 1**). Patients more likely to experience TO had a lower Charlson Comorbidity Index score (TO, 3.5 [2 – 4]; non-TO, 4 [3 – 5]; *P*=.01) and a higher estimated 10-year survival (TO, 53% [53 – 90]; non-TO, 53% [21 – 77]; *P*=.03). Patients who underwent pancreas resection were less likely to achieve a TO (TO, 17.4%; non-TO, 48.7%, *P*=.004) (**Supplementary Table 4**). Multivariable analysis showed that pancreas resection (OR 0.27, 95% CI 0.09 – 0.74, *P*=.01) was an independent predictor factor of low TO achievement.

3.7.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]) (**Figure 2a**). Actual overall survival at 1-, 3-, 5-, and 10-years was 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, and supra- and infra-diaphragmatic lymph nodes, duodenum). Median progression-free survival was not reached (95%CI 6.60 - NA) (**Figure 2b**). Actual progression-free survival at 1-, 3-, 5, and 10-years was 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 compared to patients with a CCI score >4 (*P*=.016), in patients with intra-hepatic tumor compared to patients with extra-hepatic tumor (*P*=.027), in patients with a single tumor compared to patients with multiple tumors (*P*=.007), in patients who underwent liver resection compared with those who underwent pancreatic resection *P*=.017), and in patients who achieved TO compared with those who failed (*P*=.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 (**Figure 4**).

Multivariable Cox analysis showed that not achieving TO (HR 4.20, 95% CI 1.11 – 15.94, *P*=.03) was independent risk factor of poor overall survival (**Table 5** and **Supplementary Table 5**). No independent predictor of progression-free survival was identified on multivariable analysis (**Supplementary Table 6**).

4. 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%. Textbook outcome was an independent prognostic factor of overall survival.

To our knowledge, this multicenter study is the largest in 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 performed 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.[30] 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.[31] 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.[30] 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.[30] 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.[30] 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 labelling 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.[30] 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.[30] 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,[30] 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. 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 twenty-five lymph nodes, eleven 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.[32]

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 US 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 US 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 pancreato-intestinal anastomosis (fistula, hemorrhage, infection) could explain the worse TO of pancreatic resection compared to hepatic resection.[33] 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 towards 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 selected patients who could actually benefit from liver transplantation in France, a country where this type of procedure could be commonly considered for selected patients.[34] However, two of the patients included in the present study received a liver transplantation as the first option, a strategy described for some patients in another European IPNB series.[11,25] 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 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 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.[30]

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[35] 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.[36] 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.[37]

This European series identified a surgical metric (not achieving TO) as independent predictor of poor overall survival in patients with IPNB. As 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.[36,38–41] Furthermore, tumor burden (multiplicity),[36] lymph node invasion,[39,41] perineural invasion,[40] or degree of tumor invasiveness[42] 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 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 intra-hepatic IPNBs.[7,25,35,36] The study protocol 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. Detection of intraluminal mucin by the surgeon is somewhat subjective. For this reason, analyses were carried out taking mucin found in pathology as 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.[30] 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.

5. CONCLUSIONS

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

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Declaration of competing interests

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

Data statement

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

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TITLE PAGE

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

Running head:

European multicenter study on IPNB

ABSTRACT

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 January 1, 2010, and December 31, 2020 was gathered under the auspices of the E-AHPBA. Textbook outcome was defined as non-prolonged length of hospital stay plus absence of any Clavien-Dindo grade ≥III complication, readmission, or mortality within 90 postoperative days.

Results: A total of 28 centers contributed 85 patients who underwent surgery for IPNB. Median age was 66 years (55-72), 49.4% were women and 87.1% Caucasian. Open surgery was performed in 72 patients (84.7%), laparoscopic in 13 (15.3%). Textbook outcome 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 vs >4 (*P*=.016), intra- vs extra-hepatic tumor (*P*=.027), single vs multiple tumor (*P*=.007), those who underwent hepatic vs pancreatic resection (*P*=.017), or achieved vs failed textbook outcome (*P*=.029). Multivariable Cox regression analysis showed that not achieving textbook outcome (HR 4.20, 95% CI 1.11-15.94, *P*=.03) was an independent prognostic factor of poor overall survival.

Conclusions: Patients undergoing liver resection for IPNB were more likely to achieve a textbook outcome than those requiring a pancreatic resection. Comorbidity, tumor location and tumor multiplicity influenced overall survival. Textbook outcome was an independent prognostic factor of overall survival.

Keywords

Bile duct neoplasms, intraductal precursor lesion, surgical resection, textbook outcome, pancreas

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

Abbreviations

ASA, American Society of Anesthesiology

BilIN, biliary intra-epithelial neoplasia

CCI, Charlson comorbidity index

CT, computed tomography

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

ECOG, Eastern Cooperative Oncology Group

ERCP, endoscopic retrograde cholangio-pancreatography

EUS, endoscopic ultrasonography

HPB, hepato-pancreato-biliary

ICU, intensive care unit

IPNB, intraductal papillary neoplasm of the bile duct

IQR, inter-quartile range

MRI, magnetic resonance imaging

TO, textbook outcome

US, ultrasonography

1. 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 intra- and/or extra-hepatic 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- and high-grade, the latter being more frequent.[2] Depending on the type of epithelial cell, it is sub-classified 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 3 out of 4 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 <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 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.

2. PATIENTS AND METHODS

2.1.Study Design

This is an observational retrospective study of patients with IPNB lesions undergoing elective HPB surgery between January 1, 2010, and December 31, 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 December 2, 2021, and waived the informed consent of patients due to the retrospective nature of the study (PR[AG]469/2021). The study is registered in 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.[15] 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 was carried out according to the STROCCS Reporting Guidelines for Cohort Studies.[16]

2.2.Demographics, baseline characteristics, and diagnosis

In addition to demographic data and past surgical history, body mass index, ASA score, ECOG performance status, Charlson comorbidity index (CCI),[17] biliary symptoms,

serum bilirubin and CA-19.9 level, and presence of hepatolithiasis or clonorchis infestation were recorded. The contribution of preoperative imaging tests (CT, MRI, transabdominal US, ERCP, EUS, endoscopic cholangioscopy, percutaneous transhepatic cholangiography) used to identify IPNB lesions was assessed.

2.3.Intraoperative events and surgical procedures

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.[18] 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 pancreatectomy was performed.

2.4.Postoperative course

Length of ICU and hospital stay, and 90-day morbidity and mortality according to the Clavien-Dindo classification were recorded.[19] Bile leak,[20] post-hepatectomy liver failure,[21] postoperative hemorrhage,[22] pancreatic fistula,[23] delayed gastric emptying,[24] according to ISGLS or ISGPS, and other major medical complications were identified. Any additional procedures (radiological, endoscopic, or surgical) performed during index hospitalization, episodes of ICU readmission, hospital readmission, or reintervention during the first 90 days were recorded.

2.5.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 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.[25] The epithelial cells were classified as gastric, oncocytic, pancreatobiliary, or intestinal.[8,11] Additional features included 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.[26] Involvement of the resection margin of the cystic duct, common bile duct and parenchyma was examined.[27]

2.6.Textbook outcomes

The TO was defined based on the absence of all of the following: prolonged length of hospital stay (a length of hospital stay ≥75th percentile of the total cohort), 90-day Clavien-Dindo grade ≥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.

2.7.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.

2.8.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, US) hosted at Asociación Española de Gastroenterología (AEG; www.redcap.aegastro.es).[28]

2.9.Analysis

Descriptive statistics were used for demographic and baseline characteristics of patients. Quantitative variables are reported as median and interquartile range (IQR), and categorical variables as absolute and relative frequencies. Differences between groups of patients were compared using the Chi-square test or Fisher´s exact test for categorical data, the T-test for parametric quantitative data, and the Mann-Whitney U test for quantitative non-parametric data. Cohen's *kappa* coefficient was used to describe and measure inter-observer 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 date of surgery and date of death or last follow-up. Progression-free survival was defined by the interval between date of surgery and date of recurrence diagnosis, or last follow-up or death in patients without recurrence.[29] 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 .10 on univariable analysis were entered into a multivariable model. *P* values of less than .05 were considered statistically significant. All analyses were performed using RStudio, version 1.2.5001 (Integrated Development for R. RStudio, Inc., Boston, MA, USA).

3. RESULTS

3.1.Demographic and baseline characteristics

A total of 28 centers contributed 85 patients who underwent surgery for IPNB between January 1, 2010 and December 31, 2020, with a median (IQR) of 2 (1 – 4) patients per center (**Supplementary Table 1**). Demographics and baseline characteristics are presented in **Table 1**. 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 ECOG performance status 0 (57.6%). Patients had a median Charlson comorbidity index score of 4 (2 – 5) and an estimated median 10-year survival of 53% (21 – 77). One third of patients (35.3%) had 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.

3.2.Preoperative work-up and management

A representative MRI image of an IPNB is shown in **Supplementary Figure 1a**. Preoperative imaging tests, their diagnostic performance, and imaging findings are summarized in **Supplementary Table 2**. As an example, 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 a transhepatic access in five.

3.3.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 units. Liver resection was performed in 49 patients (57.6%). 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**.

3.4.Postoperative course

After surgery, 53 patients (62.4%) spent two 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 ≥III complication occurred in 32.9% of patients, mortality was 7.1%, 17 patients (20.0%) were readmitted to the hospital for seven 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%).

3.5.Pathology report

A representative photomicrograph of an IPNB is shown in **Supplementary Figure 1b**. 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**). 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%), 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 were harvested from 61 patients (71.8%). In 11 of these patients, a median of three (2 – 4) involved lymph nodes per patient were identified.

3.6.Textbook outcomes

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 was 32.0% after pancreas resection (**Figure 1**). Patients more likely to experience TO had a lower Charlson Comorbidity Index score (TO, 3.5 [2 – 4]; non-TO, 4 [3 – 5]; *P*=.01) and a higher estimated 10-year survival (TO, 53% [53 – 90]; non-TO, 53% [21 – 77]; *P*=.03). Patients who underwent pancreas resection were less likely to achieve a TO (TO, 17.4%; non-TO, 48.7%, *P*=.004) (**Supplementary Table 4**). Multivariable analysis showed that pancreas resection (OR 0.27, 95% CI 0.09 – 0.74, *P*=.01) was an independent predictor factor of low TO achievement.

3.7.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]) (**Figure 2a**). Actual overall survival at 1-, 3-, 5-, and 10-years was 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, and supra- and infra-diaphragmatic lymph nodes, duodenum). Median progression-free survival was not reached (95%CI 6.60 - NA) (**Figure 2b**). Actual progression-free survival at 1-, 3-, 5, and 10-years was 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 compared to patients with a CCI score >4 (*P*=.016), in patients with intra-hepatic tumor compared to patients with extra-hepatic tumor (*P*=.027), in patients with a single tumor compared to patients with multiple tumors (*P*=.007), in patients who underwent liver resection compared with those who underwent pancreatic resection *P*=.017), and in patients who achieved TO compared with those who failed (*P*=.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 (**Figure 4**).

Multivariable Cox analysis showed that not achieving TO (HR 4.20, 95% CI 1.11 – 15.94, *P*=.03) was independent risk factor of poor overall survival (**Table 5** and **Supplementary Table 5**). No independent predictor of progression-free survival was identified on multivariable analysis (**Supplementary Table 6**).

4. 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%. Textbook outcome was an independent prognostic factor of overall survival.

To our knowledge, this multicenter study is the largest in 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 performed 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.[30] 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.[31] 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.[30] 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.[30] 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.[30] 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 labelling 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.[30] 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.[30] 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,[30] 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. 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 twenty-five lymph nodes, eleven 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.[32]

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 US 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 US 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 pancreato-intestinal anastomosis (fistula, hemorrhage, infection) could explain the worse TO of pancreatic resection compared to hepatic resection.[33] 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 towards 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 selected patients who could actually benefit from liver transplantation in France, a country where this type of procedure could be commonly considered for selected patients.[34] However, two of the patients included in the present study received a liver transplantation as the first option, a strategy described for some patients in another European IPNB series.[11,25] 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 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 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.[30]

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[35] 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.[36] 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.[37]

This European series identified a surgical metric (not achieving TO) as independent predictor of poor overall survival in patients with IPNB. As 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.[36,38–41] Furthermore, tumor burden (multiplicity),[36] lymph node invasion,[39,41] perineural invasion,[40] or degree of tumor invasiveness[42] 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 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 intra-hepatic IPNBs.[7,25,35,36] The study protocol 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. Detection of intraluminal mucin by the surgeon is somewhat subjective. For this reason, analyses were carried out taking mucin found in pathology as 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.[30] 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.

5. CONCLUSIONS

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

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Declaration of competing interests

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

Data statement

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

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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	13 (15.3)
• Liver resection	1 (1.2)
• Pancreatic resection	0
• Bile duct surgery	2 (2.4)
• Other supra-mesocolic surgery	1 (1.2)
• Infra-mesocolic surgery	11 (12.9)
Past medical history-liver related, n (%)	
• Primary biliary cirrhosis	1 (1.2)
• Autoimmune hepatitis	2 (2.4)
• Primary sclerosing cholangitis	3 (3.5)
• Alcohol related cirrhosis	0
• Hepatitis B virus	2 (2.4)
• Hepatitis C virus	0
• Other	4 (4.7)
Preoperative symptoms, n (%)	
• Asymptomatic	22 (25.9)
• Abdominal pain	34 (40.0)
• Jaundice	38 (44.7)
• Acute cholangitis	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

☐, *items with multiple possible answers*

Table 2. Intra-operative 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 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)
Peri-operative 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 / Non-anatomical	3 (3.5)
• Left lateral sectionectomy (2 & 3)	4 (4.7)
• Left hemi-hepatectomy (2, 3 & 4)	26 (30.6)
• Right hemi-hepatectomy (5, 6, 7 & 8)	5 (5.9)
• Extended right hepatectomy (4, 5, 6, 7 & 8)	5 (5.9)
• Extended left hepatectomy (2, 3, 4, 5 & 8)	2 (2.4)
• Segment 4 wedge resection	2 (2.4)
• Segment 5 wedge resection	1 (1.2)
• Anatomical resection segment 1	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	61 (71.8)
• Bile duct resection + hepatico-jejunostomy	53 (62.4)
• Intraoperative cholangioscopy	5 (5.9)
• Intraoperative cholangiography	6 (7.1)
• Other bile duct surgical procedure	5 (5.9)

• *, items with multiple possible answers*

Table 3. Post-operative 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)
Intra-abdominal 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)

Table 4. Pathology report

	Patients, n = 85
Localization of the lesion(s), n (%)	
Intrahepatic	44 (51.8)
Extrahepatic above cystic duct	27 (31.8)
Extrahepatic below cystic duct	31 (36.5)
Number of lesions, n (%)	
Single	65 (76.5)
Multiple	20 (23.5)
Diameter of largest lesion, mm, median (IQR)	20 (15 - 33)
Presence of mucin, n (%)	27 (31.8)
Local communication with 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	3 (3.5)
• Common bile duct	9 (10.6)
• Parenchymal	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)

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 value**
Textbook outcome		
Achieved	1 [Reference]	
Failed	4.20 (1.11 – 15.94)	.03

FIGURES

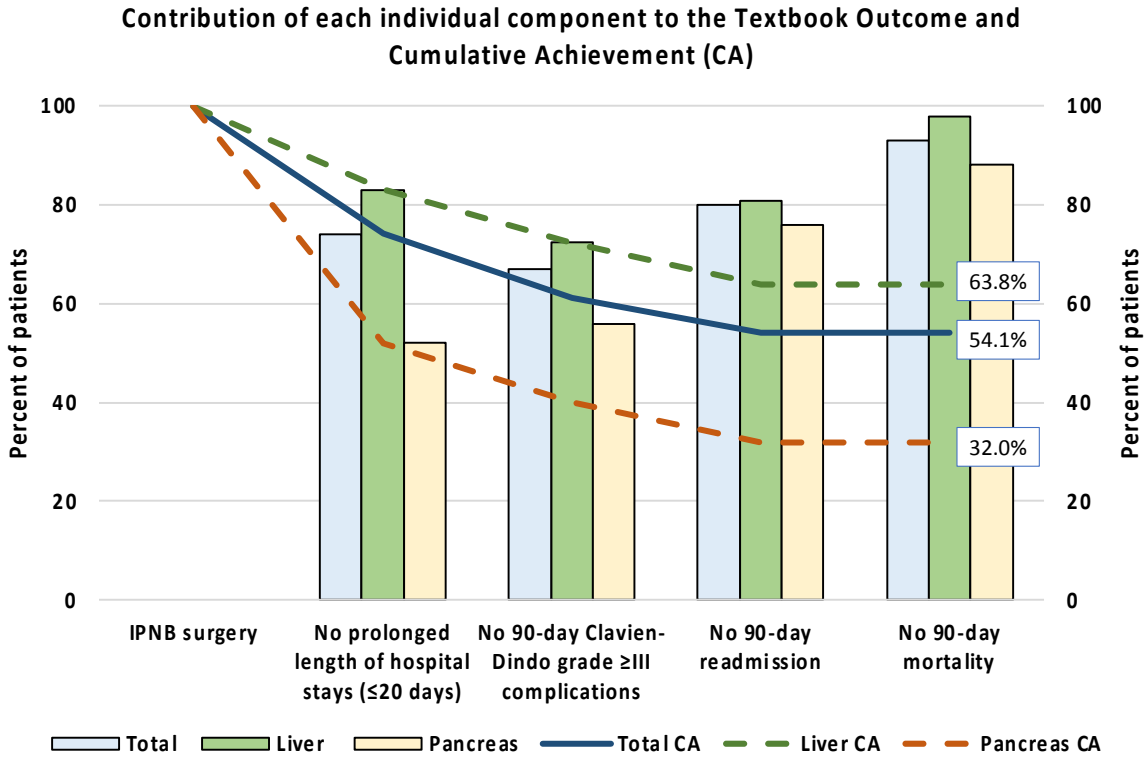

Figure 1. Textbook outcome for all patients (blue bars), and patients stratified into liver (green bars) and pancreas (yellow bars) surgery for IPNB. The contribution of each individual component (horizontal axis) to the textbook outcome (bars) and to the cumulative achievement (CA) (lines) are represented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

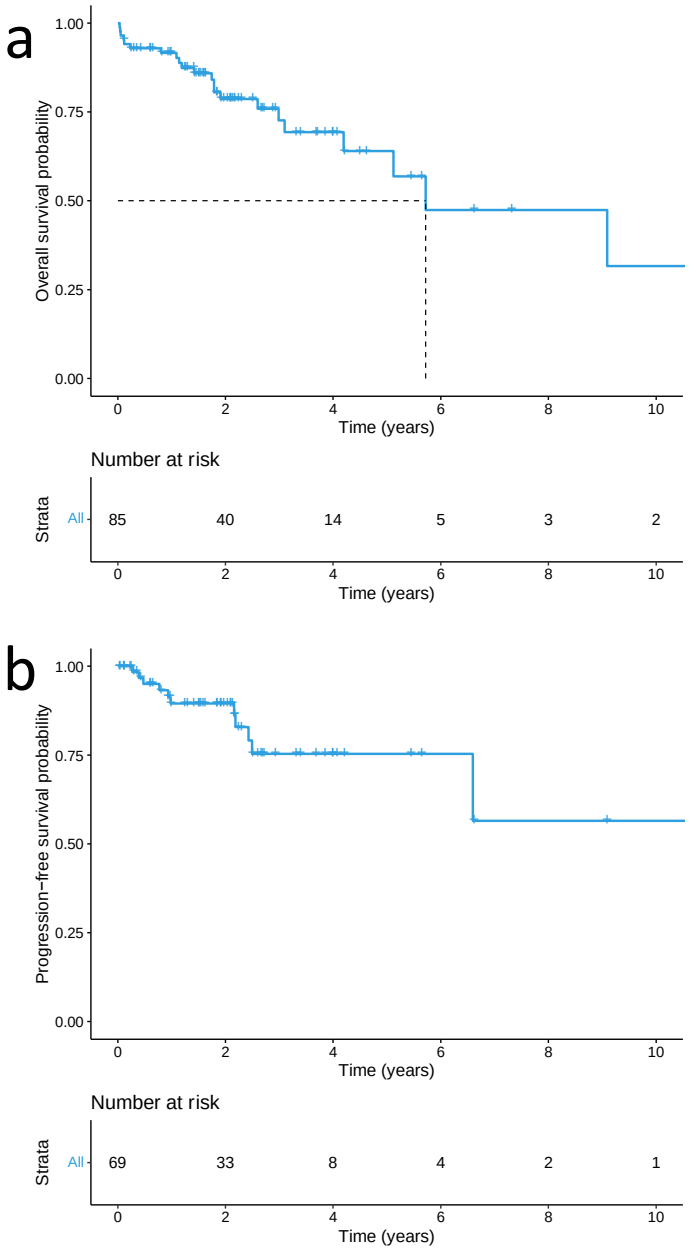

Figure 2. Overall survival (a) and progression-free survival (b) of patients who underwent surgery for IPNB depicted using the Kaplan-Meier curve. The shaded areas represent the 95% confidence interval. Dotted lines indicate median overall survival (median progression-free survival was not reached).

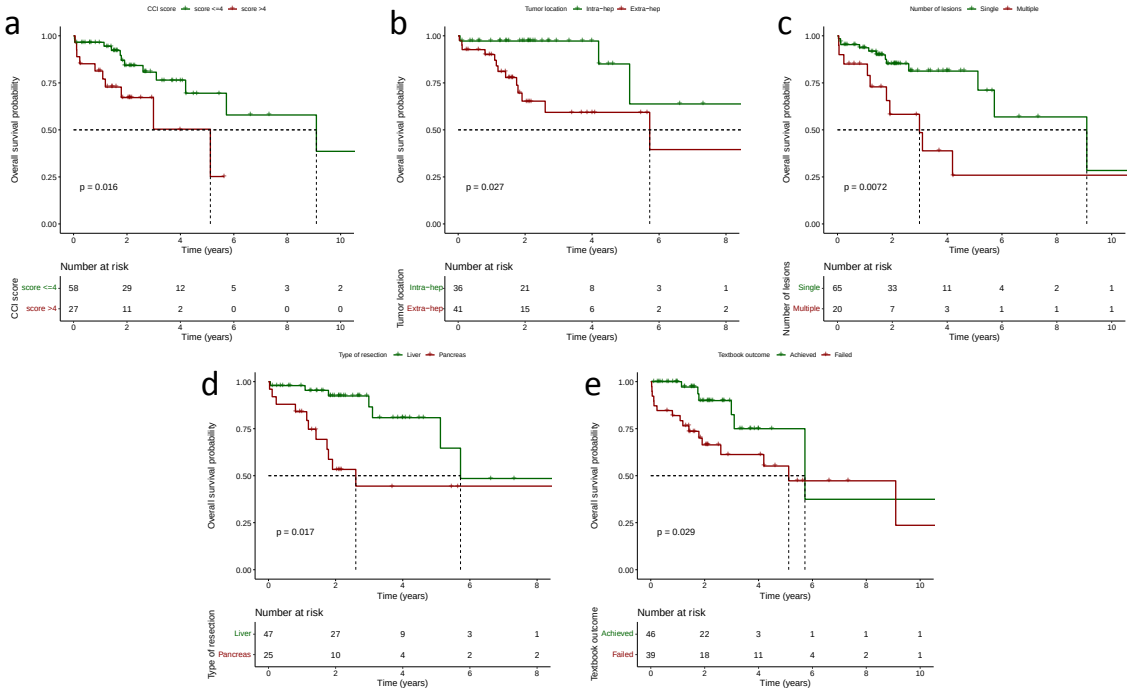

Figure 3. Overall survival of patients who underwent surgery for IPNB is depicted using Kaplan-Meier curves. The shaded areas represent the 95% confidence interval. Dotted lines indicate median survival. Log-rank analysis was performed based on: **a)** Charlson Comorbidity Index (CCI score ≤4 vs >4), **b)** tumor location (intra- vs extra-hepatic), **c)** tumor burden at presentation (single vs multiple tumors), **d)** type of resection (liver vs pancreas), and **e)** textbook outcome achievement.

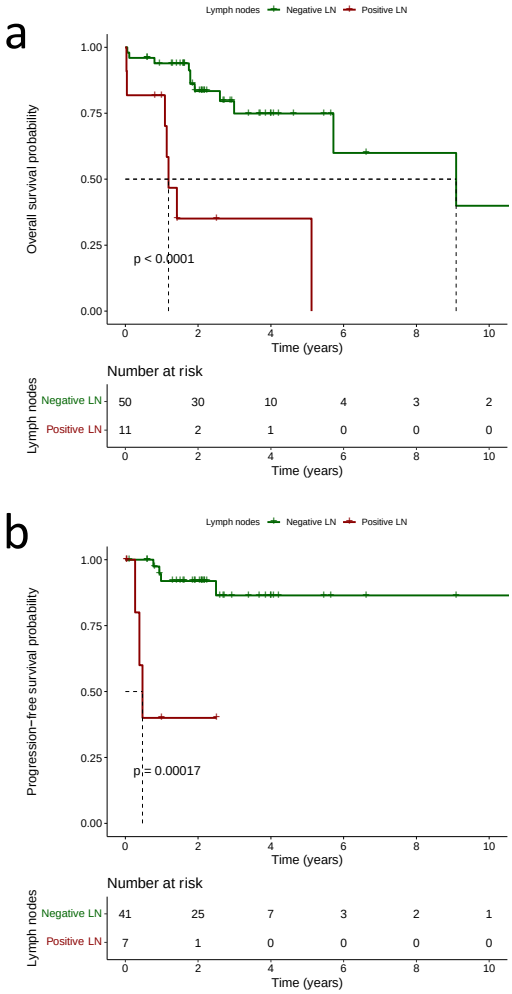

Figure 4. Overall survival **(a)** and progression-free survival **(b)** of patients who underwent lymph node dissection for IPNB, depicted using the Kaplan-Meier curve. The shaded areas represent the 95% confidence interval. Dotted lines indicate median survival (median progression-free survival was not reached in patients with negative lymph nodes).

TITLE PAGE

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

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European multicenter study on IPNB

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ABSTRACT

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 January 1, 2010, and December 31, 2020 was gathered under the auspices of the E-AHPBA. Textbook outcome was defined as non-prolonged length of hospital stay plus absence of any Clavien-Dindo grade ≥III complication, readmission, or mortality within 90 postoperative days.

Results: A total of 289 centers contributed 856 patients who underwent surgery for IPNB. Median age was 66 years (55-72), 49.48.8% were women and 87.16% Caucasian. Open surgery was performed in 723 patients (84.79%), laparoscopic in 13 (15.31%). Textbook outcome was achieved in 54.17% of patients, reaching 63.8% after liver resection, and 32.04.6% after pancreas resection. Median overall survival was 5.72 years, with 5-year overall survival of 63% (95% CI 5049-821). Overall survival was better in patients with Charlson comorbidity score ≤4 vs >4 (*P*=.016), intra- vs extra-hepatic tumor (*P*=.027), single vs multiple tumor (*P*=.007), those who underwent hepatic vs pancreatic resection (*P*=.017), or achieved vs failed textbook outcome (*P*=.029). Multivariable Cox regression analysis showed that ethnicity other than Caucasian (HR 7.79, 95% CI 1.60-37.99, *P*=.01), Charlson comorbidity score >4 (HR 3.94, 95% CI 1.30-11.95, *P*=.02), not achieving textbook outcome (HR 4.205.13, 95% CI 1.1135-15.949.51, *P*=.032), and multiple tumors (HR 3.33, 95% CI 1.06-10.47, *P*=.04) werewas an independent risk prognostic factors of poor overall survival.

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Conclusions: Patients undergoing liver resection for IPNB were more likely to achieve a textbook outcome than those requiring a pancreatic resection. Comorbidity, tumor location and tumor multiplicity influenced overall survival. Textbook outcome was an ~~Ethnicity, comorbidity, and tumor multiplicity were~~ independent prognostic factor~~s~~ of overall survival.

Keywords

Bile duct neoplasms, intraductal precursor lesion, surgical resection, textbook outcome, pancreas

Highlights

- Intraductal papillary neoplasia of the bile duct is a rare disease in Western countries
- This European study examine~~d~~d~~s~~ the outcomes of 85~~6~~ patients operated on for this tumor
- Comorbidity, tumor location and tumor multiplicity influenced overall survival
- ~~Fifty-four percent of patients experienced textbook outcome after surgical resection~~
- Textbook outcome achievement rate was higher after hepatic than pancreatic resection

- ~~Ethnicity, comorbidity, and tumor multiplicity~~Textbook outcome was a ~~were~~ prognostic factor~~s~~ of overall survival

Abbreviations

ASA, American Society of Anesthesiology

BilIN, biliary intra-epithelial neoplasia

CCI, Charlson comorbidity index

CT, computed tomography

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

ECOG, Eastern Cooperative Oncology Group

ERCP, endoscopic retrograde cholangio-pancreatography

EUS, endoscopic ultrasonography

HPB, hepato-pancreato-biliary

ICU, intensive care unit

IPNB, intraductal papillary neoplasm of the bile duct

IQR, inter-quartile range

MRI, magnetic resonance imaging

TO, textbook outcome

US, ultrasonography

1. 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 intra- and/or extra-hepatic 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- and high-grade, the latter being more frequent.[2] Depending on the type of epithelial cell, it is sub-classified 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 3 out of 4 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 <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 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 ~~textbook outcome (~~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.

2. PATIENTS AND METHODS

2.1.Study Design

This is an observational retrospective study of patients with IPNB lesions undergoing elective HPB surgery between January 1, 2010, and December 31, 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 December 2, 2021, and waived the informed consent of patients due to the retrospective nature of the study (PR[AG]469/2021). The study is registered in 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.[15] 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 was carried out according to the STROCCS Reporting Guidelines for Cohort Studies.[16]

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2.2.Demographics, baseline characteristics, and diagnosis

In addition to demographic data and past surgical history, body mass index, ASA score, ECOG performance status, Charlson comorbidity index (CCI),[17] biliary symptoms,

serum bilirubin and CA-19.9 level, and presence of hepatolithiasis or clonorchis infestation were recorded. The contribution of preoperative imaging tests (CT, MRI, transabdominal US, ERCP, EUS, endoscopic cholangioscopy, percutaneous transhepatic cholangiography) used to identify IPNB lesions was assessed.

2.3.Intraoperative events and surgical procedures

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.[18] 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 pancreatectomy was performed.

2.4.Postoperative course

Length of ICU and hospital stay, and 90-day morbidity and mortality according to the Clavien-Dindo classification were recorded.[19] Bile leak,[20] post-hepatectomy liver failure,[21] postoperative hemorrhage,[22] pancreatic fistula,[23] delayed gastric emptying,[24] according to ISGLS or ISGPS, and other major medical complications were identified. Any additional procedures (radiological, endoscopic, or surgical) performed during index hospitalization, episodes of ICU readmission, hospital readmission, or reintervention during the first 90 days were recorded.

2.5.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 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.[25] The epithelial cells were classified as gastric, oncocytic, pancreatobiliary, or intestinal.[8,11] Additional features included 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.[26] Involvement of the resection margin of the cystic duct, common bile duct and parenchyma was examined.[27]

2.6.Textbook outcomes

The TO was defined based on the absence of all of the following: prolonged length of hospital stay (a length of hospital stay ≥75th percentile of the total cohort), 90-day Clavien-Dindo grade ≥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.

2.7.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.

2.8.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, US) hosted at Asociación Española de Gastroenterología (AEG; www.redcap.aegastro.es).[28]

2.9.Analysis

Descriptive statistics were used for demographic and baseline characteristics of patients. Quantitative variables are reported as median and interquartile range (IQR), and categorical variables as absolute and relative frequencies. Differences between groups of patients were compared using the Chi-square test or Fisher´s exact test for categorical data, the T-test for parametric quantitative data, and the Mann-Whitney U test for quantitative non-parametric data. Cohen's *kappa* coefficient was used to describe and measure inter-observer 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 date of surgery and date of death or last follow-up. Progression-free survival was defined by the interval between date of surgery and date of recurrence diagnosis, or last follow-up or death in patients without recurrence.[29] 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 .10 on univariable analysis were entered into a multivariable model. *P* values of less than .05 were considered statistically significant. All analyses were performed using RStudio, version 1.2.5001 (Integrated Development for R. RStudio, Inc., Boston, MA, USA).

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3. RESULTS

3.1.Demographic and baseline characteristics

A total of 2~~8~~9 centers contributed 8~~5~~6 patients who underwent surgery for IPNB between January 1, 2010 and December 31, 2020, with a median (IQR) of 2 (1 – 4) patients per center (**Supplementary Table 1**). Demographics and baseline characteristics are presented in **Table 1**. Median age of patients was 66 years (55 – 72), 4~~9.4~~8.8% were women, 8~~7.1~~6% Caucasian, with a BMI of 25.8 (23.1 – 28.2). Most had ASA score II (6~~1.2~~0.5%) and ECOG performance status 0 (5~~7.6~~8.1%). Patients had a median Charlson comorbidity index score of 4 (2 – 5) and an estimated median 10-year survival of 53% (21 – 77). One third of patients (3~~5.3~~6%) had history of abdominal surgery, and a few had a history of liver disease. Abdominal pain, jaundice and cholangitis were the main symptoms. Bilirubin was ~~slightly~~ elevated, and CA-19.9 was mostly within normal limits. Hepatolithiasis was found in two (2.~~4~~3%) patients and Clonorchis infestation in none.

3.2.Preoperative work-up and management

A representative MRI image of an IPNB is shown in **Supplementary Figure 1a**. Preoperative imaging tests, their diagnostic performance, and imaging findings are summarized in **Supplementary Table 2**. As an example, diagnostic sensitivity of CT and MRI was only 1~~7.3~~8.5% and 35.5%, respectively. Slightly more than half of the patients (5~~5.3~~4.7%) had intrahepatic IPNB. Imaging tests detected extrahepatic IPNB involving the bile duct upstream of the confluence with the cystic duct in 26 patients

(30.62%) and/or distal in 323 patients (37.68.4%), and pancreatic involvement in 112 patients (12.94.0%). Imaging tests detected a single tumor in 678 patients (78.89.1%), multifocal in 18 (21.20.9%), and a size of 20 mm (15.58 - 30.0) for the largest tumor (missing size data for 22 patients). In 212 patients (24.75.6%), a preoperative biopsy compatible with IPNB was obtained. Preoperative biliary drainage was performed in 29 patients, endoscopically in 24 and percutaneously via a transhepatic access in five.

3.3.Intraoperative details and surgical procedures

An open approach was performed in 723 patients (84.79%) and a laparoscopic approach in 13 (15.31%) (**Table 2**). An intraoperative event was recorded in seven patients (8.31%), 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 (21.20.9%). Median operative time was 3575 min (2540 – 4280). Median estimated intraoperative blood loss was 300 mL (16375 – 500), and intraoperative transfusion was administered to 189 patients (21.22.1%), who received a median of two (2 – 3.5) pRBC units each. Liver resection was performed in 49 patients (57.60%). The types of liver resection are detailed in **Table 2**. Liver transplantation was performed in five patients (5.98%), in two as the primary treatment, and in three as a salvage surgical procedure. Pancreatoduodenectomy was performed in 26 patients (30.62%), total pancreatectomy in two one (1.22.3%). Bile duct procedures are detailed in **Table 2**.

3.4.Postoperative course

After surgery, 534 patients (62.48%) spent two days (1 – 5) in the ICU (**Table 3**). The median length of hospital stay was 11 days (6 – 2019). 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 ≥III complication occurred in 32.96% of patients, mortality was 7.1%, 17 patients (20.019.8%) were readmitted to the hospital for seven days (3 – 12), and 12 patients (14.10%) 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%).

3.5.Pathology report

A representative photomicrograph of an IPNB is shown in **Supplementary Figure 1b**. Pathology data are shown in **Table 4**. According to pathology reports, 44 patients (51.82%) had intrahepatic IPNB; extrahepatic IPNB involving the bile duct was present cranial to the confluence with the cystic duct in 27 patients (31.84%) and/or caudal in 312 patients (36.57.2%). Pathology reports showed a single tumor in 656 patients (76.57%), multiple tumors in 20 patients (23.53%), and a size of 20 mm (15 - 332) for the largest lesion. Mucin was found in 27 patients (31.84%). 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**). 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 (69.48%). Finally, Tis was diagnosed in 38 patients (44.72%). Stromal, vascular, lymphatic, perineural invasion, or neuroendocrine differentiation was found in 16, 9, 910, 134 and 1 patients, respectively. Most resections were R0 (81.24%), incomplete resections were distributed among the resection margins of the cystic duct, common bile duct or parenchyma. A median of six lymph nodes (2 – 167) per patient were harvested from 612 patients (71.82.1%). In 112 of these patients, a median of three (2 – 4) involved lymph nodes per patient were identified.

3.6.Textbook outcomes

To define TO, the 75th percentile of length of hospital stays (2019 days) was chosen. Overall, TO was achieved in 467 of 856 patients (54.17%), a figure that varied according to the type of surgery: it reached 63.8% in liver surgery and was 32.04.6% after pancreas resection (**Figure 1**). Patients more likely to experience TO had a lower Charlson Comorbidity Index score (TO, 3.54 [2 – 4]; non-TO, 4 [3 – 5]; *P*=.01) and a higher estimated 10-year survival (TO, 53% [5337 – 90]; non-TO, 53% [21 – 77]; *P*=.034). Patients who underwent pancreas resection were less likely to achieve a TO (TO, 17.49.1%; non-TO, 48.7%, *P*=.0047) (**Supplementary Table 4**). Multivariable analysis showed that pancreas resection (OR 0.279, 95% CI 0.0910 – 0.748, *P*=.012) was an independent predictor factor of low TO achievement.

3.7.Survival analysis

Median follow-up was 23 months (14 – 37.74). During the follow-up period, 2223 patients (25.96.7%) died. Median overall survival was 5.72 years (95% CI 4.19 – not reached [NA]) (**Figure 2a**). Actual overall survival at 1-, 3-, 5-, and 10-years was 92% (95% CI 86 – 98), 7332% (9556% CI 6110 – 8665), 63% (95% CI 5049 – 8221), and 31% (95% CI 12 – 8110), respectively. Recurrence was detected in 167 patients, single location in nine eight and multiple in eight; the liver was affected in 11 patients, bile ducts and pancreas in one, respectively, and other locations in eight seven (lung, peritoneum, and supra- and infra-diaphragmatic lymph nodes, duodenum). Median progression-free survival was not reached (95%CI 6.60 - NA) (**Figure 2b**). Actual progression-free survival at 1-, 3-, 5, and 10-years was 9088% (95% CI 8220 – 9887), 754% (95% CI 6221 – 9110), 754% (95% CI 6221 – 9110), and 5776% (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 Caucasian patients compared to other ethnicities (*P*=.04), in patients with a CCI score ≤4 compared to patients with a CCI score >4 (*P*=.016008), in patients with a single tumor compared to patients with multiple tumors (*P*=.011), and in patients with intra-hepatic tumor compared to patients with extra-hepatic tumor (*P*=.027018), in patients with a single tumor compared to patients with multiple tumors (*P*=.007), in patients who underwent liver resection compared with those who underwent pancreatic resection *P*=.017), and in patients who achieved TO compared with those who failed (*P*=.029). There was no difference in overall survival according to the presence of mucin, degree of atypia, epithelial cell type, T stage, or resection

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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 (**Figure 4**).

Multivariable Cox analysis showed that ~~ethnicity other than Caucasian (being Asian/African/Latino) (HR 7.79, 95% CI 1.60 – 37.99, *P*=.01), Charlson comorbidity score >4 (HR 3.94, 95% CI 1.30 – 11.95, *P*=.02),~~ not achieving TO (HR 4.20~~5.13~~, 95% CI 1.11~~35~~ – 15.94~~9.51~~, *P*=.03~~2~~)~~,~~ ~~and multiple tumors (HR 3.33, 95% CI 1.06 – 10.47, *P*=.04) were~~ was independent risk factor~~s~~ of poor overall survival (**Table 5** and **Supplementary Table 5**). No independent predictor of progression-free survival was identified on multivariable~~t~~ analysis (**Supplementary Table 6**).

4. DISCUSSION

In summary, IPNB is a rare disease in Western countries. Over half (54.17%) of patients experienced a ~~textbook outcome~~TO after IPNB resection, a proportion that was higher after hepatic resection (63.8%) and lower after pancreatic resection (32.0~~4.6~~%). Median overall survival was 5.72 years, and 5-year overall survival was 63%. ~~Ethnicity, comorbidity,~~ T~~t~~extbook outcome ~~, and tumor multiplicity~~ was an~~ere~~ independent prognostic factor~~s~~ of overall survival.

To our knowledge, this multicenter study is the largest in 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 performed complex HPB surgery and even liver transplantation. Unlike the Asian series, 87.1~~6~~% 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.[30] 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.[31] 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.[30] 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.[30] 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.[30] In the present series, 69.48% 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 labelling 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.[30] 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.[30] In our series, 76.57% were single and 23.5% multiple. Finally, in the systematic review, 22% of patients underwent pancreatectomy as the only surgical procedure,[30] while 312.8% 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. 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 twenty-five lymph nodes, eleven 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.[32]

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 US 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~~1~~% and reported that 54.1~~7~~% of patients experienced a TO. A study of Medicare administrative data in the US 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~~4.6~~% 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 731% decreased odds of TO achievement among patients who underwent surgical resection for IPNB. High morbidity associated with pancreato-intestinal anastomosis (fistula, hemorrhage, infection) could explain the worse TO of pancreatic resection compared to hepatic resection.[33] 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 towards 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 selected patients who could actually benefit from liver transplantation in France, a country where this type of procedure could be commonly considered for selected patients.[34] However, two of the patients included in the present study received a liver transplantation as the first option, a strategy described for some patients in another European IPNB series.[11,25] 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 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 5049 – 8241), data that are in line with survival in other geographic regions with a higher 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.[30]

CEthnicity, comorbidity, two tumor characteristics (location, number of tumors) and the resected organ (liver or pancreas) influenced 5-year overall survival in this European study. Similarly, a study by Matsumoto et al[35] showed that patients with intrahepatic IPNBs had better postoperative recurrence-free survival than patients with extrahepatic IPNBs, and multiple IPNBs had poorer 5-year survival than single IPNBs in a study from Korea.[36] In our study, patients who underwent hepatic resection achieved better 5-year 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 5-year 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.[37]

This European series identified ~~a demographic trait (non-Caucasian ethnicity), baseline comorbidity status (CCI score >4),~~ a surgical metric (not achieving TO)~~, and tumor burden (multiplicity)~~ as independent predictor~~s~~ of poor overall survival in patients with IPNB. As novel finding~~s~~, the association of ~~non-Caucasian ethnicity with poor overall survival does not have a simple explanation and could be multifactorial, while the association with comorbidities and~~ failure to achieve ~~textbook outcome~~TO seems both predictable and informative. ~~Multiplicity was the only tumor-related prognostic factor for overall survival in this European series.~~ 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.[36,38–41] Furthermore, tumor burden (multiplicity),[36] lymph node invasion,[39,41] perineural invasion,[40] or degree of tumor invasiveness[42] 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 (2~~8~~7.3~~9~~%) in our series, although it was not reported in 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~~2~~ patients (12.9~~4.12~~%) with IPNB, an apparently low proportion but [37]similar to that described in several series, more frequent in extra- than intra-hepatic IPNBs.[7,25,35,36] The study protocol 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. Detection of intraluminal mucin by the surgeon is somewhat subjective. For this reason, analyses were carried out taking mucin found in pathology as 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.[30] 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.

5. CONCLUSIONS

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

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Declaration of competing interests

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

Data statement

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

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Table 1. Demographic and baseline characteristics

	Patients, n = 85	Patients, n = 86
Age, years, median (IQR)	66 (55 - 72)	66 (56 – 72)
Gender, n (%)		
Male	43 (50.6)	44 (51.2)
Female	42 (49.4)	42 (48.8)
Ethnicity, n (%)		
Asian	3 (3.5)	3 (3.5)
Caucasian	74 (87.1)	74 (86.0)
African	4 (4.7)	4 (4.7)
Latin	4 (4.7)	5 (5.8)
BMI, kg/m^2, median (IQR)	25.8 (23.1 - 28.2)	25.8 (23 – 28.2)
ASA score, n (%)		
I	12 (14.1)	12 (14.0)
II	52 (61.2)	52 (60.5)
III	20 (23.5)	21 (24.4)
IV	0	0
V	0	0
Unknown	1 (1.2)	1 (1.2)
ECOG performance status, n (%)		
0	49 (57.6)	50 (58.1)
1	30 (35.3)	30 (34.9)
2	6 (7.1)	6 (7.0)
3	0	0
4	0	0
Charlson Comorbidity Index (CCI)		
Score, median (IQR)	4 (2 - 5)	4 (2 – 5)
Estimated 10-year survival, %, median (IQR)	53 (21 - 77)	53 (21 – 77)
Past surgical history, n (%)	30 (35.3)	31 (36.0)
• Cholecystectomy	13 (15.3)	13 (15.1)
• Liver resection	1 (1.2)	1 (1.2)
• Pancreatic resection	0	0
• Bile duct surgery	2 (2.4)	2 (2.3)
• Other supra-mesocolic surgery	1 (1.2)	1 (1.2)
• Infra-mesocolic surgery	11 (12.9)	12 (14.0)
Past medical history-liver related, n (%)		
• Primary biliary cirrhosis	1 (1.2)	1 (1.2)
• Autoimmune hepatitis	2 (2.4)	2 (2.3)
• Primary sclerosing cholangitis	3 (3.5)	3 (3.5)
• Alcohol related cirrhosis	0	0
• Hepatitis B virus	2 (2.4)	2 (2.3)
• Hepatitis C virus	0	0
• Other	4 (4.7)	5 (5.8)
Preoperative symptoms, n (%)		
• Asymptomatic	22 (25.9)	23 (26.7)
• Abdominal pain	34 (40.0)	34 (39.5)
• Jaundice	38 (44.7)	38 (44.2)
• Acute cholangitis	19 (22.4)	19 (22.1)
Preoperative lab, median (IQR)		
Bilirubin, mg/dL	4.3 (1 - 9)	3.7 (1 – 9)
CA 19.9, U/mL	19 (6.0 - 63.7)	19.5 (6 – 75)
Associated conditions, n (%)		
Hepatolithiasis	2 (2.4)	2 (2.3)
Clonorchis infestation	0	0

☐, *items with multiple possible answers*

Table 2. Intra-operative details and surgical procedures

	Patients, n = 85	**Patients, n = 86**
Surgical approach, n (%)		
Open	72 (84.7)	73 (84.9)
Laparoscopic	13 (15.3)	13 (15.1)
Intraoperative events (Satava), n (%)		
No intraoperative events	78 (91.8)	79 (91.9)
Excessive blood loss, damage (no conversion)	5 (5.9)	5 (5.8)
Conversion or major change to planned operation	2 (2.4)	2 (2.3)
Intraoperative death	0	0
Intraluminal mucin, n (%)	18 (21.2)	18 (20.9)
Operative time, min, median (IQR)	357 (254 - 428)	355 (250 – 420)
Estimated blood loss, mL, median (IQR)	300 (163 - 500)	300 (175 – 500)
Peri-operative pRBC transfusion, n (%)	18 (21.2)	19 (22.1)
pRBC units transfused, median (IQR)	2 (2 - 3)	2 (2 -3.5)
Liver resection, n (%)	49 (57.6)	49 (57.0)
Type of liver resection, n (%)		
• Atypical / Non-anatomical	3 (3.5)	3 (3.5)
• Left lateral sectionectomy (2 & 3)	4 (4.7)	4 (4.7)
• Left hemi-hepatectomy (2, 3 & 4)	26 (30.6)	26 (30.2)
• Right hemi-hepatectomy (5, 6, 7 & 8)	5 (5.9)	5 (5.8)
• Extended right hepatectomy (4, 5, 6, 7 & 8)	5 (5.9)	5 (5.8)
• Extended left hepatectomy (2, 3, 4, 5 & 8)	2 (2.4)	2 (2.3)
• Segment 4 wedge resection	2 (2.4)	2 (2.3)
• Segment 5 wedge resection	1 (1.2)	1 (1.2)
• Anatomical resection segment 1	11 (12.9)	11 (12.8)
Liver transplantation, n (%)	5 (5.9)	5 (5.8)
Pancreas resection, n (%)		
Pancreatoduodenectomy	26 (30.6)	26 (30.2)
Total pancreatectomy	1 (1.2)	2 (2.3)
Bile duct procedures, n (%)		
• Cholecystectomy	61 (71.8)	61 (70.9)
• Bile duct resection + hepatico-jejunostomy	53 (62.4)	53 (61.6)
• Intraoperative cholangioscopy	5 (5.9)	5 (5.8)
• Intraoperative cholangiography	6 (7.1)	6 (7.0)
• Other bile duct surgical procedure	5 (5.9)	5 (5.8)

• , *items with multiple possible answers*

Table 3. Post-operative course

	Patients, n = 85	Patients, n = 86
ICU admission, n (%)	53 (62.4)	54 (62.8)
Length of ICU stay, days	2 (1 - 5)	2 (1 – 5)
Length of hospital stay, days	11 (6 - 20)	11 (6 – 19)
90-day postop complications, Clavien-Dindo, n (%)		
I	37 (43.5)	37 (43.0)
II	20 (23.5)	21 (24.4)
III-a	11 (12.9)	11 (12.8)
III-b	6 (7.1)	6 (7.0)
IV-a	2 (2.4)	2 (2.3)
IV-b	3 (3.5)	3 (3.5)
V	6 (7.1)	6 (7.0)
Bile leak, n (%)	13 (15.3)	13 (15.1)
Grades A / B / C	3 / 5 / 5	3 / 5 / 5
Liver failure, n (%)	7 (8.2)	7 (8.1)
Grades A / B / C	2 / 3 / 2	2 / 3 / 2
Postoperative hemorrhage, n (%)	12 (14.1)	12 (14.0)
Grades I / II / III	3 / 2 / 7	3 /2 / 7
Postoperative pancreatic fistula, n (%)	13 (15.3)	14 (16.3)
Biochemical leak / grades B / C	4 / 7 / 2	4 / 8 / 2
Delayed gastric emptying, n (%)	17 (20.0)	17 (19.8)
Grades A / B / C	6 / 9 / 2	6 / 9 / 2
Other complications, n (%)		
Cardiac arrest	1 (1.2)	1 (1.2)
Pulmonary embolism	2 (2.4)	2 (2.3)
Stroke	1 (1.2)	1 (1.2)
Intra-abdominal abscess	10 (11.8)	11 (12.8)
Urinary tract infection	2 (2.4)	2 (2.3)
Additional procedures during initial hospitalization, n (%)	14 (16.5)	15 (17.4)
Radiological / endoscopic / surgical	6 / 2 / 9	7 / 2 / 9
ICU readmission, n (%)	7 (8.2)	7 (8.1)
Length of ICU readmission, days, median (IQR)	12 (7 - 19)	12 (7 – 19)
Hospital readmission within 90 days, n (%)	17 (20.0)	17 (19.8)
Length of stay during readmission, days, median, n (IQR)	7 (3 - 12)	7 (3 – 12)
Reoperation within initial 90 days, n (%)	12 (14.1)	12 (14.0)

Table 4. Pathology report

	Patients, n = 85	Patients, n = 86
Localization of the lesion(s), n (%)		
Intrahepatic	44 (51.8)	44 (51.2)
Extrahepatic above cystic duct	27 (31.8)	27 (31.4)
Extrahepatic below cystic duct	31 (36.5)	32 (37.2)
Number of lesions, n (%)		
Single	65 (76.5)	66 (76.7)
Multiple	20 (23.5)	20 (23.3)
Diameter of largest lesion, mm, median (IQR)	20 (15 - 33)	20 (15 – 32)
Presence of mucin, n (%)	27 (31.8)	27 (31.4)
Local communication with adjacent bile duct, n (%)	43 (50.6)	44 (51.2)
Biliary intraepithelial neoplasia (BilIN), n (%)		
BilIN-1	14 (16.5)	14 (16.3)
BilIN-2	6 (7.1)	6 (7.0)
BilIN-3	4 (4.7)	4 (4.7)
Unknown	61 (71.8)	62 (72.1)
Degree of atypia, n (%)		
Low-grade dysplasia	21 (24.7)	21 (24.4)
High-grade dysplasia	14 (16.5)	14 (16.3)
Adenoma	3 (3.5)	3 (3.5)
Carcinoma in situ	11 (12.9)	11 (12.8)
Invasive carcinoma	36 (42.4)	37 (43.0)
Type of epithelial cells, n (%)		
Intestinal	17 (20.0)	17 (19.8)
Pancreatic-biliary	59 (69.4)	60 (69.8)
Gastric	8 (9.4)	8 (9.3)
Oncocytic	1 (1.2)	1 (1.2)
T stage, n (%)		
Tis	38 (44.7)	38 (44.2)
T1	21 (24.7)	21 (24.4)
T2	20 (23.5)	21 (24.4)
T3	4 (4.7)	4 (4.7)
T4	0	0
NA	2 (2.4)	2 (2.3)
Invasion, n, yes / no / unknown		
Stromal	16 / 59 / 10	16 / 59 / 11
Vascular	9 / 69 / 7	9 / 70 / 7
Lymphatic	9 / 64 / 12	10 / 64 / 12
Perineural	13 / 62 / 10	14 / 62 / 10
Neuroendocrine differentiation, n, yes / no / unknown	1 / 67 / 17	1 / 68 / 17
Resection margin status, n (%)		
R0	69 (81.2)	70 (81.4)
R1	14 (16.5)	14 (16.3)
R2	1 (1.2)	1 (1.2)
Unknown	1 (1.2)	1 (1.2)
Resection margin positive, n (%)		
• Cystic duct	3 (3.5)	3 (3.5)
• Common bile duct	9 (10.6)	9 (10.5)
• Parenchymal	4 (4.7)	4 (4.7)
Lymph nodes harvested		
Patients, n (%)	61 (71.8)	62 (72.1)
Number, median (IQR)	6 (2 - 16)	6 (2 – 17)
Lymph nodes affected		
Patients, n (%)	11 (12.9)	12 (14.0)
Number, median (IQR)	3 (2 - 4)	3 (2 – 4)

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 value**
Textbook outcome		
Achieved	1 [Reference]	
Failed	4.20 (1.11 – 15.94)	.03
	~~Multivariable~~	
~~Factors~~	~~Hazard ratio (95% CI)~~	~~P value~~
~~Ethnicity~~		
~~Caucasian~~	~~1 [Reference]~~	
~~Asian / African / Latin~~	~~7.79 (1.60 – 37.99)~~	~~.01~~
~~Charlson Comorbidity score >4~~	~~3.94 (1.30 – 11.95)~~	~~.02~~
~~Textbook outcome~~		
~~Achieved~~	~~1 [Reference]~~	
~~Failed~~	~~5.13 (1.35 – 19.51)~~	~~.02~~
~~Number of lesions~~		
~~Single~~	~~1 [Reference]~~	
~~Multiple~~	~~3.33 (1.06 – 10.47)~~	~~.04~~

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FIGURES

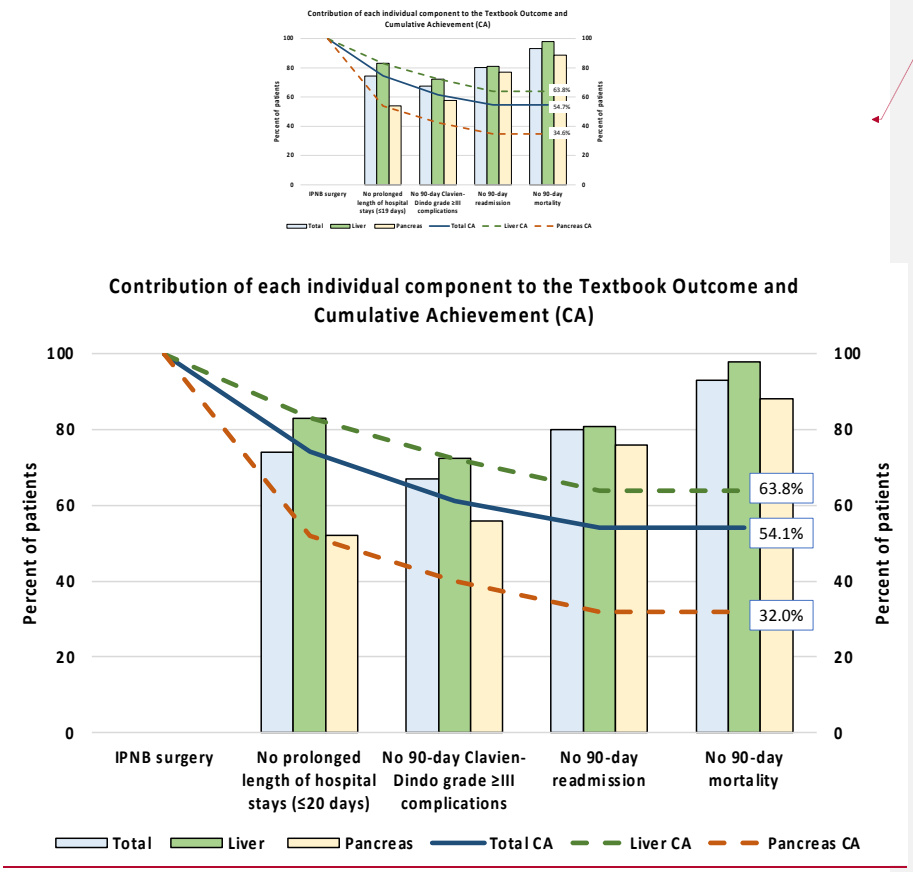

Figure 1. Textbook outcome for all patients (blue bars), and patients stratified into liver (green bars) and pancreas (yellow bars) surgery for IPNB. The contribution of each individual component (horizontal axis) to the textbook outcome (bars) and to the cumulative achievement (CA) (lines) are represented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

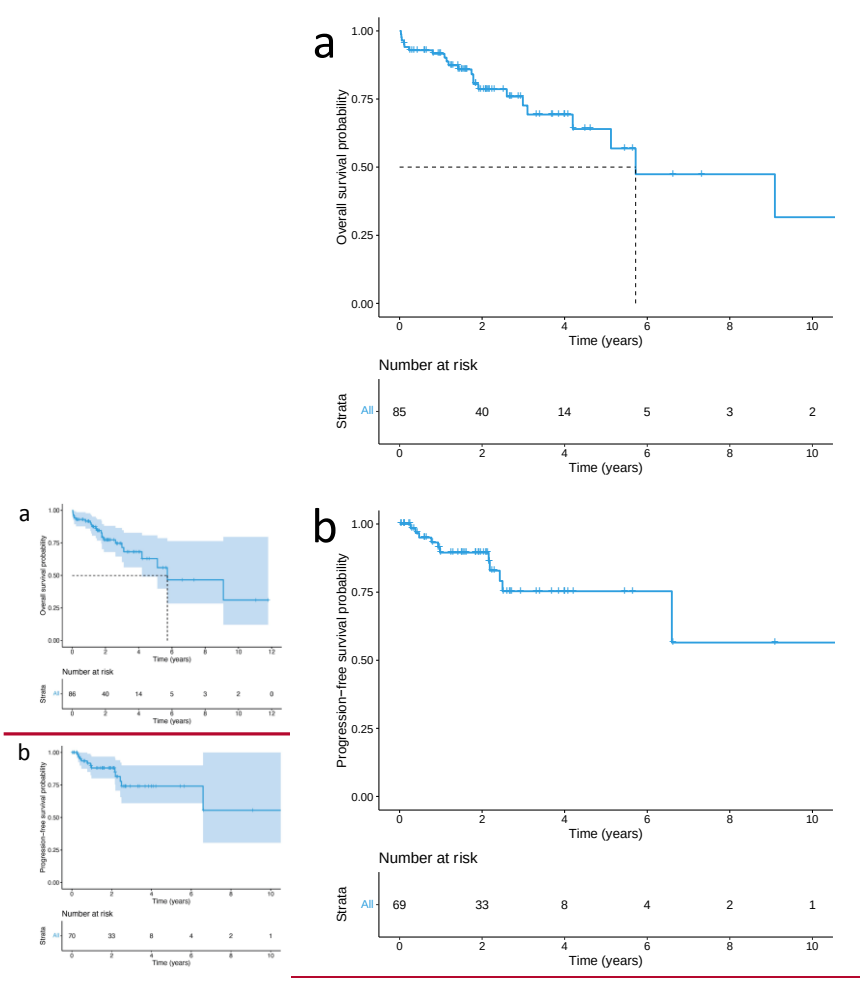

Figure 2. Overall survival (a) and progression-free survival (b) of patients who underwent surgery for IPNB depicted using the Kaplan-Meier curve. The shaded areas represent the 95% confidence interval. Dotted lines indicate median overall survival (median progression-free survival was not reached).

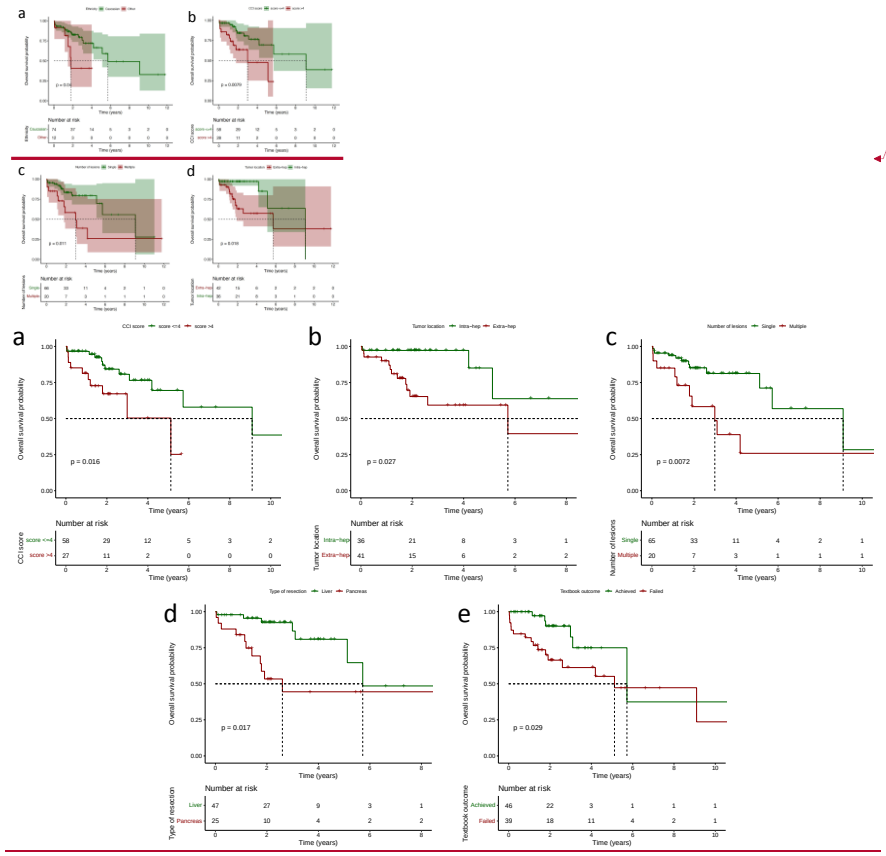

Figure 3. Overall survival of patients who underwent surgery for IPNB is depicted using Kaplan-Meier curves. The shaded areas represent the 95% confidence interval. Dotted lines indicate median survival. Log-rank analysis was performed based on: **a)** Charlson Comorbidity Index (CCI score ≤4 vs >4), **b)** tumor location (intra- vs extra-hepatic), **c)** tumor burden at presentation (single vs multiple tumors), **d)** type of resection (liver vs pancreas), and **e)** textbook outcome achievement.

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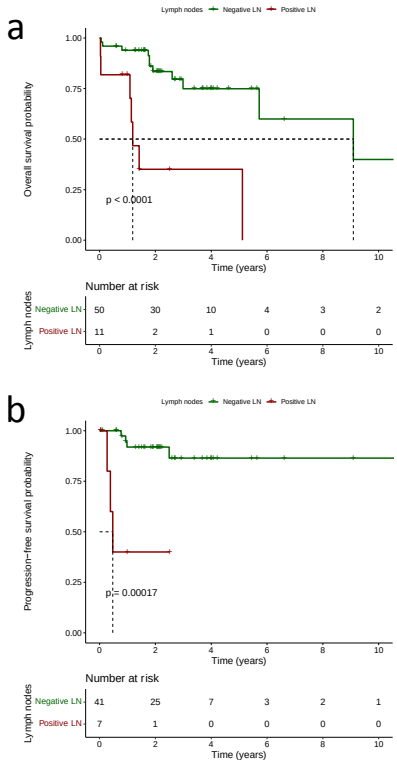

~~ethnicity (Caucasian vs Asian / African / Latin), **b)** Charlson Comorbidity Index (CCI score ≤4 vs >4), **c)** tumor burden at presentation (single vs multiple tumors), and **d)** tumor location (intra- vs extra-hepatic).~~

Figure 4. Overall survival **(a)** and progression-free survival **(b)** of patients who underwent lymph node dissection for IPNB, depicted using the Kaplan-Meier curve. The shaded areas represent the 95% confidence interval. Dotted lines indicate median survival (median progression-free survival was not reached in patients with negative lymph nodes).

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Supplementary Information

Supplementary Table 1. Patients contributed by each participating center

Supplementary Table 2. Preoperative imaging

Supplementary Table 3. Concordance between diagnoses of tumor location, tumor multiplicity and presence of mucin, as provided by Imaging, Surgery and Pathology, described and measured according to Cohen's kappa coefficient (κ)

Supplementary Table 4. Demographic and clinical factors of patients undergoing surgery for IPNB, and pathology factors of IPNB tumors, ranked by Textbook Outcome achievement. Logistic regression analysis of factors associated with Textbook Outcome achievement.

Supplementary Table 5. Univariable and multivariable Cox analysis of prognostic factors associated with Overall Survival (OS) for patients with intraductal papillary neoplasm of the bile duct (IPNB) who underwent surgical resection (n = 86)

Supplementary Table 6. Univariable and multivariable Cox analysis of prognostic factors associated with Progression-free Survival (PFS) for patients with intraductal papillary neoplasm of the bile duct (IPNB) who underwent surgical resection with an R0 margin (n = 70)

Supplementary Figure 1. **a**) Magnetic resonance imaging (post-contrast coronal T1 weighted images at the venous phase) showing an intraductal papillary neoplasm of the intrapancreatic common bile duct (white arrows); cranially, the common hepatic duct is visualized (white arrowheads). **b**) Intraductal papillary neoplasm (center left) arising from the bile duct (black arrows), H&E, 40 x (*Courtesy of Andrew Renshaw, MD*)

Supplementary Table 1. Patients contributed by each participating center

Center	Patients
Cambridge University Hospital, United Kingdom	4
Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal	3
Centro Hospitalar Universitário do Porto, Porto, Portugal	1
CHU Lieje, Lieje, Belgium	2
Clinic and University Virgen de la Arrixaca Hospital, Murcia, Spain	3
Cruces University Hospital, Bilbao, Spain	6
Dr. Balmis General University Hospital, Alicante, Spain	1
General Hospital of Athens Laiko, Athens, Greece	2
Hopital Beaujon, Clichy, France	15
Hospital Dr. Peset, Valencia, Spain	2
~~Hospital Universitario Puerta del Mar, Cádiz, Spain~~	~~1~~
Hospital Universitario Valdecilla, Santander, Spain	1
Hospital Vall d´Hebron, Barcelona, Spain	5
Hygeia Hospital, Athens, Greece	1
Karolinska University Hospital, Stockholm, Sweden	6
Linköping University, Linköping, Sweden	1
Miami Cancer Institute, Miami, Florida, United States	1
Miguel Servet University Hospital, Zaragoza, Spain	4
Nicosia General Hospital, Nicosia, Cyprus	1
Oslo University Hospital, Oslo, Norway	1
Queen Elizabeth Hospital, Birmingham, United Kingdom	6
Quirúrgica Cirujanos Asociados, Barcelona, Spain	1
Semmelweis University, Budapest, Hungary	2
Skane University Hospital, Lund University, Lund, Sweden	3
Universitas Academic Hospital, University of the Free State, Bloemfontein, South Africa	1
University Hospital Ghent, Ghent, Belgium	3
University Hospital of Besançon, Besançon, France	3
University Medical Center Groningen, Groningen, The Netherlands	4
Wits University, Johannesburg, South Africa	2
Total	**8~~5~~6**

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Supplementary Table 2. Preoperative imaging

	Patients, n = 86	**Patients, n = 85**
IPNB diagnosis, n diagnostic tests / n tests performed (%)		
• CT scan	15/81 (18.5)	14/81 (17.3)
• MRI	22/62 (35.5)	22/62 (35.5)
• Trans-abdominal US	4/43 (9.3)	3/42 (7.1)
• ERCP	17/40 (42.5)	17/40 (42.5)
• EUS	14/26 (53.8)	13/25 (52.0)
• Endoscopic cholangioscopy	10/13 (76.9)	10/13 (76.9)
• Percutaneous trans-hepatic cholangiography	1/5 (20.0)	1/5 (20.0)
Imaging findings, n (%)		
• Mass	43 (50.0)	43 (50.6)
• Ductal ectasia	13 (15.1)	13 (15.3)
• Ductal stenosis	18 (20.9)	18 (21.2)
• Ductal dilatation	38 (44.2)	38 (44.7)
• Papillary tumor	36 (41.9)	35 (41.2)
• Hyperechoic nodules	1 (1.2)	1 (1.2)
Location, n (%)		
• Intrahepatic	47 (54.7)	47 (55.3)
• Extrahepatic above merging with cystic duct	26 (30.2)	26 (30.6)
• Extrahepatic below merging with cystic duct	33 (38.4)	32 (37.6)
Pancreas affected, n (%)	12 (14.0)	11 (12.9)
Tumor, n (%)		
Single	68 (79.1)	67 (78.8)
Multifocal	18 (20.9)	18 (21.2)
Size of the single tumor or the largest lesion, mm	20 (15.8 – 30)	20 (15.5 - 30.0)
Preoperative biopsy compatible with IPNB, n (%)	22 (25.6)	21 (24.7)
Preoperative biliary drainage, n (%)	29 (33.7)	29 (34.1)
Endoscopic drainage	24 (27.9)	24 (28.2)
Percutaneous trans-hepatic drainage	5 (5.8)	5 (5.9)

• , *items with multiple possible answers*

Supplementary Table 3. Concordance between diagnoses of tumor location, tumor multiplicity and presence of mucin, as provided by Imaging, Surgery and Pathology, described and measured according to Cohen's *kappa* coefficient (κ)

	Pathology		
Imaging	Extrahepatic	Intra-hepatic	Sum
Extra-hepatic	378	1	389
Intra-hepatic	4	43	47
Sum	412	44	856

kappa coefficient = 0.88, almost perfect

	Pathology		
Imaging	Multiple tumors	Single tumor	Sum
Multiple tumors	16	2	18
Single tumor	4	634	678
Sum	20	656	856

kappa coefficient = 0.80, substantial strength of agreement

	Pathology		
Surgery	No mucin	Mucin	Sum
No mucin	567	11	678
Mucin	2	16	18
Sum	589	27	856

kappa coefficient = 0.61, substantial strength of agreement

	Pathology		
Imaging	Extrahepatic	Intra-hepatic	Sum
Extra-hepatic			
Intra-hepatic			
Sum			

kappa coefficient = 0.88, almost perfect

	Pathology		
Imaging	Multiple tumors	Single tumor	Sum
Multiple tumors			
Single tumor			
Sum			

kappa coefficient = 0.80, substantial strength of agreement

	Pathology		
Surgery	No mucin	Mucin	Sum
No mucin			
Mucin			
Sum			

kappa coefficient = 0.61, substantial strength of agreement

Supplementary Table 4. Demographic and clinical factors of patients undergoing surgery for IPNB, and pathology factors of IPNB tumors, ranked by Textbook Outcome achievement. Logistic regression analysis of factors associated with Textbook Outcome achievement.

Factors	Textbook Outcome			Univariable		Multivariable	
	Failed	Achieved	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Patients, n	39	47					
Age, years, median (IQR)	67 (61 -73)	64 (54 – 70)	.15	0.97 (0.94 – 1.01)	.19		
Gender, n (%)			.27				
Male	23 (59.0)	21 (44.7)		1 [Reference]			
Female	16 (41.0)	26 (55.3)		1.78 (0.76 – 4.26)	.19		
Ethnicity, n (%)			.66				
Asian	1 (2.6)	2 (4.3)		1.79 (0.17 – 39.61)	.64		
Caucasian	35 (89.7)	39 (83.0)		1 [Reference]			
African	2 (5.1)	2 (4.3)		0.90 (0.10 – 7.80)	.92		
Latin	1 (2.6)	4 (8.5)		3.59 (0.50 – 72.02)	.26		
ASA score, n (%)			.45				
I + II	27 (69.2)	37 (78.7)		1 [Reference]			
Other	12 (30.8)	10 (21.3)		0.61 (0.23 – 1.61)	.32		
ECOG performance status, n (%)			.94				
0	22 (56.4)	28 (59.6)		1 [Reference]			
Other	17 (43.6)	19 (40.4)		0.88 (0.37 – 2.08)	.77		
Charlson Comorbidity Index (CCI)							
Score, median (IQR)	4 (3 – 5)	4 (2 – 4)	.01	0.74 (0.56 – 0.96)	.028		
Estimated 10-year survival, %, median (IQR)	53 (21 – 77)	53 (37 – 90)	.04	1.015 (1.001 – 1.029)	.037		
Past surgical history, n (%)	15 (38.5)	16 (34.0)	.84	0.83 (0.34 – 2.01)	.67		
Preoperative symptoms, n (%)							
• Jaundice	21 (53.8)	17 (36.2)	.15	0.49 (0.20 – 1.15)	.10		
• Acute cholangitis	10 (25.6)	9 (19.1)	.64	0.69 (0.24 – 1.92)	.47		
Bilirubin, mg/dL, median (IQR)	6 (1.1 – 9.5)	2.8 (1 – 8.9)	.64	1.00 (0.97 – 1.03)	.97		
Tumor location, n (%)			.59				
Intrahepatic	14 (35.9)	22 (46.8)		1.57 (0.64 – 3.93)	.33		
Extrahepatic	21 (53.8)	21 (44.7)		1 [Reference]			
Both	4 (10.3)	4 (8.5)		1.00 (0.21 – 4.74)	1.0		
Liver resection, n (%)	19 (48.7)	30 (63.8)	.23	1.86 (0.79 – 4.47)	.16		
Pancreas resection, n (%)	19 (48.7)	9 (19.1)	.007	0.25 (0.09 – 0.64)	.005	0.29 (0.10 – 0.78)	.02
Number of lesions, n (%)			.46				
Single	28 (71.8)	38 (80.9)		1 [Reference]			
Multiple	11 (28.2)	9 (19.1)		0.60 (0.22 – 1.65)	.33		
Diameter of largest lesion, mm, median (IQR)	20 (15 – 30)	20 (12 – 34)	.89	1.00 (0.97 – 1.02)	.87		
Presence of mucin, n (%)	12 (30.8)	15 (31.9)	1.0	1.05 (0.42 – 2.67)	.91		
Degree of atypia, n (%)			.86				
Low-grade dysplasia	9 (23.1)	12 (25.5)		1.41 (0.48 – 4.22)	.53		
High-grade dysplasia	5 (12.8)	9 (19.1)		1.90 (0.55 – 7.21)	.32		
Adenoma	1 (2.6)	2 (4.3)		2.11 (0.19 – 47.78)	.56		
Carcinoma in situ	5 (12.8)	6 (12.8)		1.27 (0.33 – 5.10)	.73		
Invasive carcinoma	19 (48.7)	18 (38.3)		1 [Reference]			
Type of epithelial cells, n (%)			.20				
Intestinal	11 (28.2)	6 (12.8)		0.36 (0.11 – 1.09)	.08		
Pancreatic-biliary	24 (61.5)	36 (76.6)		1 [Reference]			
Gastric + Oncocytic	4 (10.3)	5 (10.6)		0.83 (0.20 – 3.66)	.80		
T stage, n (%)			.72				
Tis	16 (41.0)	22 (46.8)		1 [Reference]			
T1	10 (25.6)	11 (23.4)		0.80 (0.27 – 2.35)	.68		
T2	9 (23.1)	12 (25.5)		0.97 (0.33 – 2.90)	.96		
Other	4 (10.3)	2 (4.3)		0.36 (0.05 – 2.10)	.28		
Resection margin status, n (%)			.20				
R0	29 (74.4)	41 (87.2)		1 [Reference]			
R1	9 (23.1)	5 (10.6)		0.39 (0.11 – 1.26)	.13		

IQR: interquartile range. • : some patients presented more than one symptom

Factors	Textbook Outcome			Univariable		Multivariable	
	Failed	Achieved	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Patients, n	39	46					
Age, years, median (IQR)	67 (61 -73)	63 (54 – 69)	.11	0.92 (0.93 – 1.01)	.15		
Gender, n (%)			.23				
Male	23 (59.0)	20 (43.5)		1 [Reference]			
Female	16 (41.0)	26 (56.5)		1.87 (0.79 – 4.50)	.16		
Ethnicity, n (%)			.81				
Asian	1 (2.6)	2 (4.3)		1.79 (0.17 – 39.61)	.64		
Caucasian	35 (89.7)	39 (84.8)		1 [Reference]			
African	2 (5.1)	2 (4.3)		0.90 (0.10 – 7.80)	.92		
Latin	1 (2.6)	3 (6.5)		2.69 (0.33 – 55.80)	.40		
ASA score, n (%)			.35				
I + II	27 (69.2)	37 (80.4)		1 [Reference]			
Other	12 (30.8)	9 (10.6)		0.55 (0.20 – 1.48)	.24		
ECOG performance status, n (%)			1.0				
0	22 (56.4)	27 (58.7)		1 [Reference]			
Other	17 (43.6)	19 (41.3)		0.91 (0.38 – 2.17)	.83		
Charlson Comorbidity Index (CCI)							
Score, median (IQR)	4 (3 – 5)	3.5 (2 – 4)	.01	0.67 (0.49 – 0.88)	.01		
Estimated 10-year survival, %, median (IQR)	53 (21 – 77)	53 (53 – 90)	.03	1.016 (1.002 – 1.031)	.02		
Past surgical history, n (%)	15 (38.5)	15 (32.6)	.74	0.77 (0.32 – 1.89)	.57		
Preoperative symptoms, n (%)							
• Jaundice	21 (53.8)	17 (37.0)	.18	0.50 (0.21 – 1.19)	.12		
• Acute cholangitis	10 (25.6)	9 (19.6)	.68	0.71 (0.25 – 1.97)	.50		
Bilirubin, mg/dL, median (IQR)	6 (1.1 – 9.5)	2.9 (1 – 8.9)	.72	1.00 (0.97 – 1.03)	1.0		
Tumor location, n (%)			.54				
Intrahepatic	14 (35.9)	22 (47.8)		1.65 (0.67 – 4.15)	.20		
Extrahepatic	21 (53.8)	20 (43.5)		1 [Reference]			
Both	4 (10.3)	4 (8.7)		1.05 (0.22 – 4.99)	.95		
Liver resection, n (%)	19 (48.7)	30 (65.2)	.19	1.97 (0.83 – 4.79)	.13		
Pancreas resection, n (%)	19 (48.7)	8 (17.4)	.004	0.22 (0.08 – 0.58)	.003	0.27 (0.09 – 0.74)	.01
Number of lesions, n (%)			.50				
Single	28 (71.8)	37 (80.4)		1 [Reference]			
Multiple	11 (28.2)	9 (19.6)		0.62 (0.22 – 1.70)	.35		
Diameter of largest lesion, mm, median (IQR)	20 (15 – 30)	20 (12 – 35)	.82	1.00 (0.97 – 1.02)	.85		
Presence of mucin, n (%)	12 (30.8)	15 (32.6)	1.0	1.09 (0.44 – 2.76)	.86		
Degree of atypia, n (%)			.82				
Low-grade dysplasia	9 (23.1)	12 (26.1)		1.49 (0.51 – 4.50)	.47		
High-grade dysplasia	5 (12.8)	9 (19.6)		2.01 (0.58 – 7.67)	.28		
Adenoma	1 (2.6)	2 (4.3)		2.24 (0.20 – 50.67)	.53		
Carcinoma in situ	5 (12.8)	6 (13.0)		1.34 (0.34 – 5.43)	.67		
Invasive carcinoma	19 (48.7)	17 (37.0)		1 [Reference]			
Type of epithelial cells, n (%)			.21				
Intestinal	11 (28.2)	6 (13.0)		0.37 (0.12 – 1.12)	.09		
Pancreatic-biliary	24 (61.5)	35 (76.1)		1 [Reference]			
Gastric + Oncocytic	4 (10.3)	5 (10.9)		0.86 (0.21 – 3.77)	.83		
T stage, n (%)			.73				
Tis	16 (41.0)	22 (47.8)		1 [Reference]			
T1	10 (25.6)	11 (23.9)		0.80 (0.27 – 2.35)	.68		
T2	9 (23.1)	11 (23.9)		0.89 (0.30 – 2.68)	.83		
Other	4 (10.3)	2 (4.3)		0.36 (0.05 – 2.10)	.28		
Resection margin status, n (%)			.22				
R0	29 (74.4)	40 (87.0)		1 [Reference]			
R1	9 (23.1)	5 (10.9)		0.40 (0.11 – 1.29)	.14		

Supplementary Table 5. Univariable and multivariable Cox analysis of prognostic factors associated with Overall Survival (OS) for patients with intraductal papillary neoplasm of the bile duct (IPNB) who underwent surgical resection (n = 85~~5~~)

Factors	OS, n	Median OS, months	Univariable		Multivariable	
			Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age >66 years *	41	62.3	1.56 (0.68 – 3.60)	.29		
Gender						
Male	44	NA	1 [Reference]			
Female	42	69.6	0.99 (0.43 – 2.25)	.97		
Ethnicity						
Caucasian	74	69.6	1 [Reference]		1 [Reference]	
Asian / African / Latin	12	21.7	2.81 (1.01 – 7.83)	.048	7.79 (1.60 – 37.99)	.01
ASA score						
I + II	64	69.6	1 [Reference]			
Other	22	36.4	1.91 (0.80 – 4.57)	.15		
ECOG performance status						
0	50	69.6	1 [Reference]			
Other	36	51.0	1.09 (0.48 – 2.50)	.83		
Charlson Comorbidity Index (CCI) *						
Score >4	28	36.4	3.07 (1.29 – 7.32)	.01	3.94 (1.30 – 11.95)	.02
Estimated 10-year survival >53%	33	69.6	0.82 (0.35 – 1.91)	.64		
Past surgical history	31	51.0	1.53 (0.67 – 3.50)	.32		
Preoperative symptoms						
Jaundice	38	69.6	1.64 (0.72 – 3.77)	.24		
Acute cholangitis	19	69.6	1.14 (0.47 – 2.78)	.77		
Bilirubin >3.7 mg/dL *	43	69.6	0.85 (0.38 – 1.94)	.71		
Textbook outcome						
Achieved	47	69.6	1 [Reference]		1 [Reference]	
Failed	39	62.3	2.42 (0.98 – 5.96)	.05	5.13 (1.35 – 19.51)	.02
Tumor location						
Intrahepatic	36	110.6	1 [Reference]			
Extrahepatic	42	69.6	3.53 (1.16 – 10.79)	.03		
Liver resection	49	69.6	0.39 (0.17 – 0.92)	.03		
Pancreas resection	28	31.6	2.94 (1.27 – 6.77)	.01		
Number of lesions						
Single	66	110.6	1 [Reference]		1 [Reference]	
Multiple	20	36.4	2.82 (1.23 – 6.46)	.01	3.33 (1.06 – 10.47)	.04
Diameter of largest lesion >20 mm *	40	62.3	1.88 (0.81 – 4.36)	.14		
Presence of mucin	27	62.3	0.83 (0.34 – 2.03)	.68		
Degree of atypia						
Low-grade dysplasia	21	110.6	0.65 (0.23 – 1.83)	.41		
High-grade dysplasia	14	51.0	0.22 (0.03 – 1.68)	.14		
Adenoma	3	31.6	1.72 (0.22 – 13.39)	.61		
Carcinoma in situ	11	NA	0.55 (0.12 – 2.48)	.44		
Invasive carcinoma	37	62.3	1 [Reference]			
Type of epithelial cells						
Intestinal	17	NA	1.50 (0.58 – 3.87)	.41		
Pancreatic-biliary	60	69.6	1 [Reference]			
Gastric + Oncocytic	9	51.0	1.27 (0.29 – 5.62)	.75		
T stage						
Tis	38	110.6	1 [Reference]			
T1	21	NA	0.51 (0.11 – 2.40)	.39		
T2	21	37.7	2.14 (0.84 – 5.47)	.11		
Resection margin status						
R0	70	69.6	1 [Reference]			
R1	14	36.4	1.93 (0.75 – 4.95)	.17		

**, continuous factors were categorized according to the median value*
NA, not reached

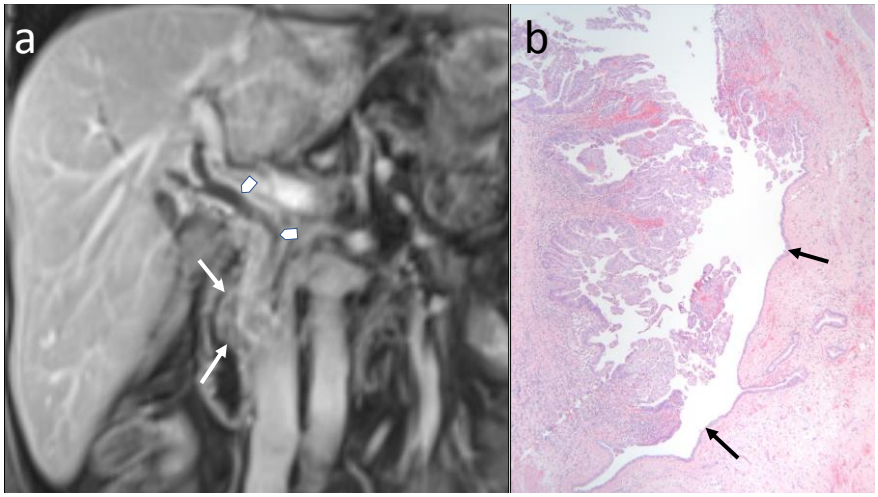
Factors	OS, n	Median OS, months	Univariable		Multivariable	
			Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age >66 years *	40	62.3	1.46 (0.62 – 3.42)	.38		
Gender						
Male	43	NA	1 [Reference]			
Female	42	69.6	1.08 (0.46 – 2.50)	.87		
Ethnicity						
Caucasian	74	69.6	1 [Reference]			
Asian / African / Latin	11	21.7	2.40 (0.79 – 7.32)	.12		
ASA score						
I + II	64	69.6	1 [Reference]			
Other	21	36.4	1.73 (0.70 – 4.31)	.24		
ECOG performance status						
0	49	69.6	1 [Reference]			
Other	36	51.0	1.17 (0.50 – 2.70)	.72		
Charlson Comorbidity Index (CCI) *						
Score >4	27	62.3	2.86 (1.18 – 6.95)	.02		
Estimated 10-year survival >53%	33	69.6	0.87 (0.37 – 2.05)	.75		
Past surgical history	30	51.0	1.40 (0.60 – 3.29)	.44		
Preoperative symptoms						
Jaundice	38	69.6	1.80 (0.77 – 4.24)	.18		
Acute cholangitis	19	69.6	1.20 (0.49 – 2.97)	.69		
Bilirubin >4.3 mg/dL *	43	69.6	0.92 (0.40 – 2.13)	.84		
Textbook outcome						
Achieved	46	69.6	1 [Reference]		1 [Reference]	
Failed	39	62.3	2.76 (1.07 – 7.13)	.04	4.20 (1.11 – 15.94)	.03
Tumor location						
Intrahepatic	36	110.6	1 [Reference]			
Extrahepatic	41	69.6	3.33 (1.08 – 10.27)	.04		
Liver resection	49	69.6	0.42 (0.18 – 0.99)	.047		
Pancreas resection	27	31.6	2.74 (1.17 – 6.42)	.02		
Number of lesions						
Single	65	110.6	1 [Reference]			
Multiple	20	36.4	3.02 (1.30 – 7.02)	.01		
Diameter of largest lesion >20 mm *	39	62.3	1.78 (0.76 – 4.19)	.19		
Presence of mucin	27	62.3	0.89 (0.36 – 2.18)	.79		
Degree of atypia						
Low-grade dysplasia	21	110.6	0.68 (0.24 – 1.95)	.47		
High-grade dysplasia	14	51.0	0.24 (0.03 – 1.83)	.17		
Adenoma	3	31.6	1.82 (0.23 – 14.31)	.57		
Carcinoma in situ	11	NA	0.60 (0.13 – 2.71)	.51		
Invasive carcinoma	36	62.3	1 [Reference]			
Type of epithelial cells						
Intestinal	17	NA	1.58 (0.61 – 4.13)	.35		
Pancreatic-biliary	59	69.6	1 [Reference]			
Gastric + Oncocytic	9	51.0	1.36 (0.30 – 6.05)	.69		
T stage						
Tis	38	110.6	1 [Reference]			
T1	21	NA	0.51 (0.11 – 2.41)	.40		
T2	20	37.7	1.95 (0.74 – 5.10)	.17		
Resection margin status						
R0	69	69.6	1 [Reference]			
R1	14	36.4	2.02 (0.78 – 5.21)	.15		

Supplementary Table 6. Univariable and multivariable Cox analysis of prognostic factors associated with Progression-free Survival (PFS) for patients with intraductal papillary neoplasm of the bile duct (IPNB) who underwent surgical resection with an R0 margin (n = 69~~70~~)

Factors	PFS, n	Median PFS, months	Univariable		Multivariable	
			Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age >66 years *	31	NA	1.09 (0.34 – 3.47)	.84		
Gender						
Male	34	NA	1 [Reference]			
Female	36	111.0	1.50 (0.45 – 5.02)	.51		
Ethnicity						
Caucasian	62	110.6	1 [Reference]			
Asian / African / Latin	8	14.4	6.89 (1.82 – 26.18)	.005		
ASA score						
I + II	52	111.0	1 [Reference]			
Other	18	NA	0.61 (0.13 – 2.80)	.53		
ECOG performance status						
0	42	111.0	1 [Reference]			
Other	28	NA	1.16 (0.37 – 3.69)	.80		
Charlson Comorbidity Index (CCI) *						
Score >4	20	NA	1.28 (0.34 – 4.86)	.72		
Estimated 10-year survival >53%	27	111.0	2.99 (0.90 – 9.97)	.07		
Past surgical history	25	111.0	1.14 (0.36 – 3.63)	.82		
Preoperative symptoms						
Jaundice	29	NA	2.08 (0.65 – 6.60)	.22		
Acute cholangitis	15	31.6	2.54 (0.77 – 8.33)	.12		
Bilirubin >3.7 mg/dL *	34	NA	1.15 (0.37 – 3.62)	.81		
Textbook outcome						
Achieved	41	NA	1 [Reference]			
Failed	29	111.0	0.79 (0.23 – 2.70)	.71		
Tumor location						
Intrahepatic	29	111.0	1 [Reference]			
Extrahepatic	36	NA	1.90 (0.55 – 6.63)	.31		
Liver resection	38	110.6	0.58 (0.18 – 1.82)	.35		
Pancreas resection	24	31.6	1.89 (0.60 – 6.00)	.28		
Number of lesions						
Single	60	110.6	1 [Reference]			
Multiple	10	26.3	1.83 (0.39 – 8.53)	.44		
Diameter of largest lesion >20 mm *	32	111.0	1.57 (0.50 – 4.90)	.44		
Presence of mucin	19	111.0	0.39 (0.08 – 1.78)	.22		
Degree of atypia						
Other	42		0.13 (0.03 – 0.58)	.008		
Invasive carcinoma	28		1 [Reference]			
Type of epithelial cells						
Intestinal	14	NA	0.34 (0.04 – 2.69)	.31		
Pancreatic-biliary	49	110.6	1 [Reference]			
Gastric + Oncocytic	7	29.6	0.99 (0.12 – 7.79)	.99		
T stage						
Tis	34	110.6	1 [Reference]			
T1	18	NA	1.94 (0.27 – 13.89)	.51		
T2	13	30.3	11.50 (2.37 – 55.84)	.002		

**, continuous factors were categorized according to the median value*
NA, not reached

Factors	PFS, n	Median PFS, months	Univariable		Multivariable	
			Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age >66 years *	30	NA	0.89 (0.26 – 3.08)	.86		
Gender						
Male	33	NA	1 [Reference]			
Female	36	80.3	1.97 (0.52 – 7.47)	.32		
Ethnicity						
Caucasian	62	NA	1 [Reference]			
Asian / African / Latin	7	11.4	4.84 (1.02 – 22.87)	.047		
ASA score						
I + II	52	NA	1 [Reference]			
Other	17	80.3	0.31 (0.04 – 2.42)	.26		
ECOG performance status						
0	41	NA	1 [Reference]			
Other	28	80.3	1.35 (0.41 – 4.44)	.63		
Charlson Comorbidity Index (CCI) *						
Score >4	19	NA	0.87 (0.19 – 4.14)	.87		
Estimated 10-year survival >53%	27	80.3	3.97 (1.05 – 15.03)	.04		
Past surgical history	24	80.3	0.91 (0.26 – 3.13)	.88		
Preoperative symptoms						
Jaundice	29	NA	2.61 (0.76 – 8.99)	.13		
Acute cholangitis	15	30.3	3.01 (0.87 – 10.42)	.08		
Bilirubin >4.3 mg/dL *	34	NA	1.40 (0.42 – 4.65)	.58		
Textbook outcome						
Achieved	40	NA	1 [Reference]			
Failed	29	NA	0.91 (0.26 – 3.23)	.88		
Tumor location						
Intrahepatic	29	NA	1 [Reference]			
Extrahepatic	35	NA	1.65 (0.46 – 5.98)	.44		
Liver resection	38	NA	0.68 (0.20 – 2.26)	.53		
Pancreas resection	23	NA	1.54 (0.45 – 5.31)	.49		
Number of lesions						
Single	59	NA	1 [Reference]			
Multiple	10	29.6	2.10 (0.44 – 10.00)	.35		
Diameter of largest lesion >20 mm *	31	NA	1.33 (0.40 – 4.40)	.64		
Presence of mucin	19	NA	0.42 (0.09 – 1.96)	.27		
Degree of atypia						
Other	42	80.3	0.14 (0.03 – 0.65)	.01		
Invasive carcinoma	27	NA	1 [Reference]			
Type of epithelial cells						
Intestinal	14	NA	0.38 (0.05 – 2.99)	.36		
Pancreatic-biliary	48	80.3	1 [Reference]			
Gastric + Oncocytic	7	29.6	1.11 (0.14 – 8.84)	.92		
T stage						
Tis	34	80.3	1 [Reference]			
T1	18	NA	1.96 (0.27 – 14.05)	.50		
T2	12	26.3	10.19 (2.04 – 50.96)	.005		



Supplementary Figure 1. **a**) Magnetic resonance imaging (post-contrast coronal T1 weighted images at the venous phase) showing an intraductal papillary neoplasm of the intrapancreatic common bile duct (white arrows); cranially, the common hepatic duct is visualized (white arrowheads). **b**) Intraductal papillary neoplasm (center left) arising from the bile duct (black arrows), H&E, 40 x (*Courtesy of Andrew Renshaw, MD*)

The STROCSS 2019 Guideline		
Item no.	**Item description**	**Page**
TITLE: Intraductal papillary neoplasms of the bile duct: A European retrospective multicenter observational study (EUR-IPNB Study)		
1	Title: - The word cohort or cross-sectional or case-controlled is included - The area of focus is described (e.g. disease, exposure/intervention, outcome) - Key elements of study design are stated (e.g. retrospective or prospective)	1
ABSTRACT		
2a	Introduction: the following points are briefly described - Background - Scientific Rationale for this study	5
2b	Methods: the following areas are briefly described - Study design (cohort, retro-/prospective, single/multi-centred) - Patient populations and/or groups, including control group, if applicable - Interventions (type, operators, recipients, timeframes) - Outcome measures	5
2c	Results: the following areas are briefly described - Summary data (with statistical relevance) with qualitative descriptions, where appropriate	5
2d	Conclusion: the following areas are briefly described - Key conclusions - Implications to practice - Direction of and need for future research	5
INTRODUCTION		
3	Introduction: the following areas are described in full - Relevant background and scientific rationale - Aims and objectives - Research question and hypotheses, where appropriate	8-9
METHODS		
4a	Registration and ethics - Research Registry number is stated, in accordance with the declaration of Helsinki* - All studies (including retrospective) should be registered before submission *"*Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject*" (this can be obtained from: ResearchRegistry.com or ClinicalTrials.gov or ISRCTN)	10
4b	Ethical Approval: the following areas are described in full - Necessity for ethical approval - Ethical approval, with relevant judgement reference from ethics committees - Where ethics was unnecessary, reasons are provided	10

4c	Protocol: the following areas are described comprehensively - Protocol (*a priori* or otherwise) details, with access directions - If published, journal mentioned with the reference provided	10-14
4d	Patient Involvement in Research - Describe how, if at all, patients were involved in study design e.g. were they involved on the study steering committee, did they provide input on outcome selection, etc.	10
5a	Study Design: the following areas are described comprehensively - 'Cohort' study is mentioned - Design (e.g. retro-/prospective, single/multi-centred)	10
5b	Setting: the following areas are described comprehensively - Geographical location - Nature of institution (e.g. academic/community, public/private) - Dates (recruitment, exposure, follow-up, data collection)	10
5c	Cohort Groups: the following areas are described in full - Number of groups - Division of intervention between groups	11-13
5d	Subgroup Analysis: the following areas are described comprehensively - Planned subgroup analyses - Methods used to examine subgroups and their interactions	11-13
6a	Participants: the following areas are described comprehensively - Eligibility criteria - Recruitment sources - Length and methods of follow-up	10-13
6b	Recruitment: the following areas are described comprehensively - Methods of recruitment to each patient group - Period of recruitment	10-13
6c	Sample Size: the following areas are described comprehensively - Margin of error calculation - Analysis to determine study population - Power calculations, where appropriate	13-14
INTERVENTION AND CONSIDERATIONS		
7a	Pre-intervention Considerations: the following areas are described comprehensively - Patient optimisation (pre-surgical measures) - Pre-intervention treatment (hypothermia/-volaemia/-tension; ICU care; bleeding problems; medications)	10-11
7b	Intervention: the following areas are described comprehensively - Type of intervention and reasoning (e.g. pharmacological, surgical, physiotherapy, psychological) - Aim of intervention (preventative/therapeutic) - Concurrent treatments (antibiotics, analgaesia, anti-emetics, NBM, VTE prophylaxis) - Manufacturer and model details where applicable	12-13
7c	Intra-Intervention Considerations: the following areas are described comprehensively - Administration of intervention (location, surgical details, anaesthetic, positioning, equipment needed, preparation, devices, sutures, operative time)	11-12

	- Pharmacological therapies include formulation, dosages, routes and durations - Figures and other media are used to illustrate	
7d	Operator Details: the following areas are described comprehensively - Training needed - Learning curve for technique - Specialisation and relevant training	10-12
7e	Quality Control: the following areas are described comprehensively - Measures taken to reduce variation - Measures taken to ensure quality and consistency in intervention delivery	13-14
7f	Post-Intervention Considerations: the following areas are described comprehensively - Post-operative instructions and care - Follow-up measures - Future surveillance requirements (e.g. imaging, blood tests)	12-14
8	Outcomes: the following areas are described comprehensively - Primary outcomes, including validation, where applicable - Definitions of outcomes - Secondary outcomes, where appropriate - Follow-up period for outcome assessment, divided by group	11-12
9	Statistics: the following areas are described comprehensively - Statistical tests, packages/software used, and interpretation of significance - Confounders and their control, if known - Analysis approach (e.g. intention to treat/per protocol) - Sub-group analysis, if any	13-14
RESULTS		
10a	Participants: the following areas are described comprehensively - Flow of participants (recruitment, non-participation, cross-over and withdrawal, with reasons) - Population demographics (prognostic features, relevant socioeconomic features, and significant numerical differences)	15
10b	Participant Comparison: the following areas are described comprehensively - Table comparing demographics included - Differences, with statistical relevance - Any group matching, with methods	14-20
10c	Intervention: the following areas are described comprehensively - Changes to interventions, with rationale and diagram, if appropriate - Learning required for interventions - Degree of novelty for intervention	16-20
11a	Outcomes: the following areas are described comprehensively - Clinician-assessed and patient-reported outcomes for each group - Relevant photographs and imaging are desirable - Confounders to outcomes and which are adjusted	16-20
11b	Tolerance: the following areas are described comprehensively - Assessment of tolerance - Loss to follow up, with reasons (percentage and fraction)	18-20

	- Cross-over with explanation	
11c	Complications: the following areas are described comprehensively - Adverse events described - Classified according to Clavien-Dindo classification* - Mitigation for adverse events (blood loss, wound care, revision surgery should be specified) *Dindo D, Demartines N, Clavien P-A. 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): 205-213	16-18
12	Key Results: the following areas are described comprehensively - Key results, including relevant raw data - Statistical analyses with significance	16-20
DISCUSSION		
13	Discussion: the following areas are described comprehensively - Conclusions and rationale - Reference to relevant literature - Implications to clinical practice - Comparison to current gold standard of care - Relevant hypothesis generation	21-25
14	Strengths and Limitations: the following areas are described comprehensively - Strengths of the study - Limitations and potential impact on results - Assessment of bias and management	25
15	Implications and Relevance: the following areas are described comprehensively - Relevance of findings and potential implications to clinical practice are detailed - Future research that is needed is described, with study designs detailed	21-24
CONCLUSION		
16	Conclusions: - Key conclusions are summarised - Key directions for future research are summarised	26
DECLARATIONS		
17a	Conflicts of interest - Conflicts of interest, if any, are described	Author disclosure form
17b	Funding - Sources of funding (e.g. grant details), if any, are clearly stated	

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories, then this should be stated.

Please state any conflicts of interest

None

Please state any sources of funding for your research

None

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

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

Research Registration Unique Identifying Number (UIN)

The World Medical Association's Declaration of Helsinki 2013 states in article 35: *'Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject'*. Editors of IJS require that all types of research studies involving human participants should be registered prospectively and failing that retrospectively. There are many places to register your research, and you can choose which is the most suitable for your needs:

•https://www.clinicaltrials.gov/ - for all human studies - free
•http://www.chictr.org.cn/index.aspx - for all human studies - free
•https://www.researchregistry.com/ - for all human studies - charge
•https://www.isrctn.com/ - for all human studies - charge
•Prospero - for systematic reviews - free
•There are many national registries approved by the UN that can be found here
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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-the-registry#home/registrationdetails/6301cd2ae0bab60023029214/

Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

CRediT authorship contribution statement

(I) Conception and design: José Manuel Ramia, Mario Serradilla-Martín, Mickaël Lesurtel.
(II) Administrative support: Mario Serradilla-Martín, Nuria Lluís, Mar Achalandabaso.
(III) Provision of study materials or patients: All authors.
(IV) Collection and assembly of data: Nuria Lluís.
(V) Data analysis and interpretation: Nuria Lluís, José Manuel Ramia, Mario Serradilla-Martín, Mar Achalandabaso, Mickaël Lesurtel.
(VI) Manuscript writing: Nuria Lluís.
(VII) Final approval of manuscript: All authors.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. Please note that providing a guarantor is compulsory.

José Manuel Ramia