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ORIGINAL ARTICLE

# Intraductal papillary neoplasms of the bile ducts: a comparative study of a rare disease in Europe and Nagoya, Japan

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## Abstract

**Background:** Intraductal papillary neoplasm of the bile ducts (IPNB) is a rare disease in Western countries. The aim of this study was to compare tumor characteristics, management strategies, and outcomes between Western and Eastern patients who underwent surgical resection for IPNB.

**Methods:** A multi-institutional retrospective series of patients with IPNB undergoing surgery between January 2010 and December 2020 was gathered under the auspices of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA), and at Nagoya University Hospital, Japan.

**Results:** A total of 85 patients (51% male; median age 66 years) from 28 E-AHPBA centers were compared to 91 patients (64% male; median age 71 years) from Nagoya. Patients in Europe had more multiple lesions (23% vs 2%, P < .001), less invasive carcinoma (42% vs 85%, P < .001), and more intrahepatic tumors (52% vs 24%, P < .001) than in Nagoya. Patients in Europe experienced less 90-day grade >3 Clavien-Dindo complications (33% vs 68%, P < .001), but higher 90-day mortality rate (7.0% vs

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0%, P = .03). R0 resections (81% vs 82%) were similar. Overall survival, excluding 90-day postoperative deaths, was similar in both regions.

**Discussion:** Despite performing more extensive resections, the low perioperative mortality rate observed in Nagoya was probably influenced by a combination of patient-, tumor-, and surgery-related factors.

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## Introduction

In 2019, the World Health Organization (WHO) updated its definition of intraductal papillary neoplasms of the liver and bile ducts (IPNB), characterizing them as a grossly visible preinvasive neoplasm with intraductal papillary or villous growth of biliary-type epithelium.[1] The WHO classification system acknowledges that IPNB can progress from low-to high-grade dysplasia, and may harbor an invasive carcinoma component. IPNB can arise in either intrahepatic or extrahepatic bile ducts, with incidences varying depending on geographic location. The highest incidence rates are found in Eastern Asian countries, where IPNB accounts for 10–38% of all bile duct tumors. In comparison, IPNB is less common in North America and in Europe. IPNB can present as a single or multiple tumors, it may cause bile duct dilatation, or even be radiographically undetectable. Although IPNB is a sporadic disease without familial aggregation, certain risk factors have been identified in Asian countries. These include sclerosing cholangitis, hepatolithiasis, and clonorchiasis.

Despite meeting the criteria to be classified as a rare disease, IPNB is not always recognized as such,[2] while a more prevalent counterpart of the pancreas—intraductal papillary mucinous neoplasm (IPMN)—is recognized.[3] This discrepancy highlights the need for greater awareness and recognition of a rare disease like IPNB to ensure that patients receive appropriate care and support.

Limited evidence on IPNB in Western countries has been published, including case reports and small cohort studies from US and Europe with less than 50 patients.[4–6] A rough estimate, based on a recent multicenter study, indicated that 6% of members of the European-African Hepato-Pancreatic-Biliary Association (E-AHPBA) managed only 85 patients with IPNB over ten years.[7] This highlights the importance of learning from the experience gained in Eastern Asian countries, where IPNB is more common but still qualifies as a rare disease. Over the past decade, approximately fifteen studies conducted in East Asia have reported survival data for a median (IQR [inter-quartile range]) of 101 (58–147) IPNB patients per study (Supplementary Table 1).[8,9,18–22,10–17] However, to the best of our knowledge, no study has yet compared patient and tumor characteristics, surgical management strategies, and long-term outcomes between IPNB patients in Western and Eastern countries.

## Patients and methods

The steering committee of the recent multicenter study sponsored by the E-AHPBA hypothesized that conducting a comparative analysis could provide valuable knowledge to improve current IPNB management strategies in the West. As a result, the committee invited the team from Nagoya, Japan, a center with extensive experience in IPNB patients, to participate in the study by providing data from their electronic medical records. The team agreed to collect the same variables that had been used in the European multicenter study in order to ensure consistency and comparability.

### Study design

This was an observational retrospective and comparative study of surgically-resected patients with IPNB between January 1, 2010, and December 31, 2020, at centers represented by members of the E-AHPBA, and at Nagoya University Graduate School of Medicine, Japan. The study protocol was approved by the ethics committee of the Vall d'Hebron Hospital, Barcelona, Spain (PR [AG]469/2021), and informed consent was waived for this Health Insurance Portability and Accountability Act (HIPAA) compliant study. Planning and analysis was carried out according to the STROCCS Reporting Guidelines for Cohort Studies.[23]




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### Demographics, baseline characteristics, and diagnosis

In addition to demographic data and past surgical history, body mass index, American Society of Anesthesiology (ASA) score, Eastern Cooperative Oncology Group (ECOG) performance status, Charlson Comorbidity Index (CCI),[24] biliary symptoms, serum bilirubin and CA-19.9 levels, and presence of hepatolithiasis or clonorchis infestation were recorded.

### Surgical procedures and intraoperative events

Surgical procedures were selected based on location and extension of tumors. In Nagoya, two standard surgical procedures were basically used in the management of patients with IPNB: 1) major hepatectomy with caudate lobectomy and resection of the extrahepatic biliary tract, and 2) pancreatoduodenectomy with complete excision of the extrahepatic biliary tract. Bile duct resection alone was an exceptional option restricted to patients with poor performance status. Hepato-pancreatoduodenectomy was undertaken in selected patients with widely extended IPNB. On the contrary, the surgical options were diverse in Europe. Intraoperative events were graded according to the Satava classification.[25] Surgical approach, as well as operative time, estimated blood loss (EBL), and need for blood product transfusion were recorded. The finding of intraluminal mucin intraoperatively was identified.

### Postoperative course

Length of intensive care unit (ICU) and hospital stay, and 90-day morbidity according to the Clavien–Dindo classification were recorded.[26] Bile leak,[27] post-hepatectomy liver failure,[28] postoperative hemorrhage,[29] pancreatic fistula,[30] delayed gastric emptying,[31] according to International Study Group of Liver (ISGLS) or Pancreatic Surgery (ISGPS), and other major medical complications were identified. Episodes of ICU or hospital readmission, or reintervention during the first 90 days were identified. Adjuvant and salvage treatments were collected. Dates of recurrence, last follow-up and death were recorded.

### Pathology

The number and diameter of the lesions and their intrahepatic or extrahepatic location were identified. In addition, 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.[1,32] Additional features included presence of intraluminal mucin, stromal, vascular, lymphatic, or perineural invasion. Involvement of the resection margin was examined.[33]

### Data collection and statistical analysis

Anonymized data were collected using Research Electronic Data Capture (REDCap) tools[34] (REDCap®, Research Electronic Data Capture, University of Vanderbilt, Nashville, Tennessee, US) hosted at Asociación Española de Gastroenterología (AEG; www.redcap.aegastro.es). Descriptive statistics were used for patient demographic, tumor characteristics, and perioperative outcomes. 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 quantitative parametric data, and the Mann–Whitney U test for quantitative non-parametric data. Overall survival (OS) was calculated from the date of surgery to the date of death from any cause or last follow-up. Progression-free survival (PFS) was defined by the interval between surgery and diagnosis of recurrence, or last follow-up or death in patients without recurrence. Survival curves were constructed by the Kaplan–Meier method and were compared using the log-rank test. 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).

## Results

### Demographic and baseline characteristics

Baseline patient characteristics are summarized in Table 1. Eighty-five patients from E-AHPBA affiliated centers and 91 patients from Nagoya were compared. Briefly, European patients were younger, most of Caucasian descent, and had higher BMI and ASA scores, worse performance status, and less comorbidities as measured by the CCI. At presentation, patients in Europe had lower CA 19.9 levels, and were more frequently symptomatic, with higher rates of painless jaundice and acute cholangitis as the initial symptoms. Only two European patients had hepatolithiasis, whereas none in Nagoya had either hepatolithiasis or Clonorchis infestation.

### Surgical procedures

A laparoscopic approach was performed in 15.3% of European patients, whereas all patients in Nagoya underwent open surgical resection. Operative time and EBL were lower in Europe. Surgical procedures and additional intraoperative findings are summarized in Table 2. A similar proportion of liver and pancreas resections were done in both cohorts, but more extensive resections, including caudate lobectomy and complete extrahepatic bile duct excisions were performed in Nagoya. Hepato-pancreatoduodenectomy was exclusively performed in Nagoya in twelve patients.

### Postoperative outcomes

Postoperative 90-day major complications occurred less frequently in European patients (Table 3). Specifically, hepato-pancreato-biliary (HPB)-related complications, including post-hepatectomy liver failure and clinically relevant postoperative pancreatic fistula were less frequent in European patients; on the other hand, hemorrhage was more frequent in Europe, whereas




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**Table 1** Demographic and baseline characteristics

| | Europe, n = 85 | Nagoya, n = 91 | P value |
|---|---|---|---|
| Age, years, median (IQR) | 66 (55–72) | 71 (67–77) | <.001 |
| Sex ratio M:F, n (%) | 43:42 (50.6:49.4) | 58:33 (63.7:36.3) | .11 |
| Ethnicity, n (%) | | | <.001 |
| Asian | 3 (3.5) | 91 (100.0) | |
| Caucasian | 74 (87.1) | 0 | |
| African | 4 (4.7) | 0 | |
| Latin | 4 (4.7) | 0 | |
| BMI, kg/m$^2$, median (IQR) | 25.8 (23.1–28.2) | 21.8 (19.9–23.6) | <.001 |
| ASA score, n (%) | | | <.001 |
| I | 12 (14.1) | 42 (46.2) | |
| II | 52 (61.2) | 49 (53.8) | |
| III | 20 (23.5) | 0 | |
| IV | 0 | 0 | |
| Unknown | 1 (1.2) | 0 | |
| ECOG performance status, n (%) | | | <.001 |
| 0 | 49 (57.6) | 84 (92.3) | |
| 1 | 30 (35.3) | 6 (6.6) | |
| 2 | 6 (7.1) | 1 (1.1) | |
| 3 | 0 | 0 | |
| 4 | 0 | 0 | |
| Charlson Comorbidity Index (CCI) | | | |
| Score, median (IQR) | 4 (2–5) | 5 (4–6) | <.001 |
| Estimated 10-year survival, %, median (IQR)[a] | 53 (21–77) | 21 (21–53) | <.001 |
| Past surgical history, n (%) | 30 (35.3) | 22 (24.2) | .15 |
| • Cholecystectomy | 13 (15.3) | 2 (2.2) | |
| • Liver resection | 1 (1.2) | 3 (3.3) | |
| • Pancreatic resection | 0 | 2 (2.2) | |
| • Bile duct surgery | 2 (2.4) | 5 (5.5) | |
| • Other supra-mesocolic surgery | 1 (1.2) | 6 (6.6) | |
| • Infra-mesocolic surgery | 11 (12.9) | 10 (11.0) | |
| Preoperative symptoms, n (%) | | | |
| • Asymptomatic | 22 (25.9) | 43 (47.3) | .01 |
| • Abdominal pain | 34 (40.0) | 23 (25.3) | .05 |
| • Jaundice | 38 (44.7) | 18 (19.8) | <.001 |
| • Acute cholangitis | 19 (22.4) | 8 (8.8) | .02 |
| Preoperative lab, median (IQR) | | | |
| Bilirubin, mg/dL | 4.3 (1.0–9.0) | 1.6 (1.0–4.3) | .01 |
| CA 19.9, U/mL | 11 (2–41) | 23 (10–50) | .002 |
| Associated conditions, n (%) | | | |
| Hepatolithiasis | 2 (2.4) | 0 | .23 |
| Clonorchis infestation | 0 | 0 | .65 |

•, items with multiple possible answers.
[a], Estimated 10-year survival according to the Charlson Comorbidity Index, is calculated based on the patient's comorbidities and is irrespective of the type of IPNB lesion.




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**Table 2** Intra-operative details and surgical procedures

| | Europe, n = 85 | Nagoya, n = 91 | P value |
|---|---|---|---|
| Surgical approach, n (%) | | | <.001 |
| Open | 72 (84.7) | 91 (100.0) | |
| Laparoscopic | 13 (15.3) | 0 | |
| Intraoperative events (Satava), n (%) | | | .48 |
| No intraoperative events | 78 (91.8) | 85 (93.4) | |
| Excessive blood loss, damage (no conversion) | 5 (5.9) | 6 (6.6) | |
| Conversion or major change to planned operation | 2 (2.4) | 0 | |
| Intraoperative death | 0 | 0 | |
| Intraluminal mucin, n (%) | 18 (21.2) | 27 (29.7) | .26 |
| Operative time, min, median (IQR) | 357 (254–428) | 514 (431–617) | <.001 |
| Estimated blood loss, mL, median (IQR) | 300 (100–500) | 860 (589–1335) | <.001 |
| Peri-operative pRBC transfusion, n (%) | 18 (21.2) | 28 (30.8) | .20 |
| pRBC units transfused, median (IQR) | 2 (2–3) | 6 (4–6) | .09 |
| Liver resection, n (%) | 49 (57.6) | 63 (69.2) | .15 |
| Type of liver resection, n (%) | | | |
| • Atypical/Non-anatomical | 3 (3.5) | 0 | |
| • Left lateral sectionectomy (2 & 3) | 4 (4.7) | 0 | |
| • Left hemi-hepatectomy (2, 3 & 4) | 26 (30.6) | 19 (20.9) | |
| • Right anterior sectionectomy (5 & 8) | 0 | 1 (1.1) | |
| • Right posterior sectionectomy (6 & 7) | 0 | 1 (1.1) | |
| • Right hemi-hepatectomy (5, 6, 7 & 8) | 5 (5.9) | 29 (31.9) | |
| • Extended right hepatectomy (4, 5, 6, 7 & 8) | 5 (5.9) | 5 (5.5) | |
| • Extended left hepatectomy (2, 3, 4, 5 & 8) | 2 (2.4) | 8 (8.8) | |
| • Segment 4 wedge resection | 2 (2.4) | 0 | |
| • Segment 5 wedge resection | 1 (1.2) | 0 | |
| • Anatomical resection segment 1 | 11 (12.9) | 61 (67.0) | |
| Pancreas resection, n (%) | | | .17 |
| Pancreatoduodenectomy | 26 (30.6) | 39 (42.9) | |
| Total pancreatectomy | 1 (1.2) | 0 | |
| Hepato-pancreatoduodenectomy | 0 | 12 (13.2) | |
| Bile duct procedures, n (%) | | | |
| • Cholecystectomy | 61 (71.8) | 74 (81.3) | |
| • Bile duct resection + hepatico-jejunostomy | 53 (62.4) | 84 (92.3) | |
| • Intraoperative cholangioscopy | 5 (5.9) | 0 | |
| • Intraoperative cholangiography | 6 (7.1) | 0 | |
| • Other bile duct surgical procedure | 5 (5.9) | 0 | |

•, items with multiple possible answers.

bile leak and delayed gastric emptying rates were similar in both cohorts. Patients in Europe had shorter hospital stays and higher 90-day readmission rates. Within the first 90 days, six patients (7.1%) died in Europe whereas there was no mortality in Nagoya.

## Pathologic analysis

More patients in Europe had intrahepatic and multiple IPNB lesions (Table 4). The diameter of the largest lesion and the proportion of patients with mucin secretion were similar in both cohorts. It is noteworthy that none of the Nagoya patients had low- or high-grade dysplasia or adenoma. Consequently, more patients from Nagoya had invasive carcinoma. Stromal, vascular, lymphatic and perineural invasion is depicted in Table 4. The proportion of patients with R0 resection was similar in both cohorts. In Europe, both the lymph node dissection rate (71.8% vs 90.1%, P < .001) and number of lymph nodes harvested were




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**Table 3** Post-operative outcomes

| | Europe, n = 85 | Nagoya, n = 91 | P value |
|---|---|---|---|
| ICU admission, n (%) | 53 (62.4) | 80 (87.9) | <.001 |
| Length of ICU stay, days, median (IQR) | 2 (1–5) | 1 (1–1) | <.001 |
| Length of hospital stay, days, median (IQR) | 11 (6–20) | 28 (20–39) | <.001 |
| 90-day postop complications, Clavien–Dindo, n (%) | | | |
| Grade ≥ 3 | 28 (32.9) | 62 (68.1) | <.001 |
| Bile leak, n (%) | 13 (15.3) | 22 (24.2) | .20 |
| Grades A/B/C | 3/5/5 | 0/22/0 | |
| Liver failure, n (%) | 7 (8.2) | 19 (20.9) | .03 |
| Grades A/B/C | 2/3/2 | 15/3/1 | |
| Postoperative hemorrhage, n (%) | 12 (14.1) | 4 (4.4) | .048 |
| Grades A/B/C | 3/2/7 | 1/3/0 | |
| Postoperative pancreatic fistula, n (%) | 13 (15.3) | 36 (39.6) | <.001 |
| Biochemical leak/grade B/grade C | 4/7/2 | 1/33/2 | |
| Delayed gastric emptying, n (%) | 17 (20.0) | 14 (15.4) | .55 |
| Grades A/B/C | 6/9/2 | 9/5/0 | |
| ICU readmission, n (%) | 6 (7.1) | 3 (3.3) | .43 |
| Hospital readmission within 90 days, n (%) | 17 (20.0) | 3 (3.3) | .001 |
| Reoperation within initial 90 days, n (%) | 12 (14.1) | 2 (2.2) | .008 |
| 90-day mortality, n (%) | 6 (7.1) | 0 | |

lower (6 [2–16] vs 11 [7–18], P = .009), but still within the standards for biliary tract malignancies. However, the number of positive lymph nodes was similar in both cohorts (Table 4).

### Adjuvant therapy, recurrence, and survival

Adjuvant chemotherapy was administered to seven patients in Europe and nine patients in Nagoya. Adjuvant external beam radiation therapy was given to two patients in each cohort. During a median follow-up of 24 (14–37) months, 17 (20%) patients in Europe experienced disease recurrence in single (n = 9) or multiple (n = 8) locations. During a median follow-up of 39 (28–37) months, 29 (31.9%) patients in Nagoya experienced disease recurrence in single (n = 15) or multiple (n = 12) locations. Sites of recurrence included the liver, bile duct, pancreas, lung, peritoneum, and supradiaphragmatic lymph nodes. Recurrence was treated in 15 patients in Europe with either salvage chemotherapy (n = 12) or surgical resection (n = 3), and in 11 patients in Nagoya with either salvage chemotherapy (n = 1), radiotherapy (n = 1), or surgical resection (n = 6). One of the nine patients with recurrence who underwent salvage surgery had a positive common bile duct resection margin in the final pathology report and a pancreatoduodenectomy was performed. The remaining eight patients had an R0 resection after the index operation. A liver recurrence occurred in seven patients and an isolated biliary recurrence was detected in one patient. Unfortunately, no data on the degree of atypia of the recurrent site or the type of procedure performed in these patients was available, except for two in whom a liver non anatomical resection was performed. Median PFS was not reached (NA) years (95% CI, 6.6 – NA) in Europe and 7.1 years (95% CI, 5.2 – NA) in Nagoya (P = .63) (Fig. 1c). Actual PFS 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, in Europe; and 92% (95% CI, 86–98), 79% (95% CI, 70–90), 63% (95% CI, 50–79), and not reached, respectively, in Nagoya.

During follow-up, 23 patients (26.7%) from Europe and 20 patients (22.0%) from Nagoya died. Median OS was 5.72 years (95% CI, 4.19–NA) in Europe and NA years (95% CI, NA–NA) in Nagoya (P = .033) (Fig. 1a). Actual OS 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, in Europe; and 97% (95% CI, 93–100), 89% (95% CI, 82–96), 69% (95% CI, 58–82), and 66% (95% CI, 54–80), respectively, in Nagoya. However, given that 90-day postoperative mortality was 7.1% in Europe and 0% in Nagoya, a subsequent analysis excluding perioperative deaths showed no difference in OS between both regions (Fig. 1b).

Next, a survival analysis was performed according to the degree of invasion. Median OS of patients with invasive carcinoma was 5.7 years (95% CI, 3.10–NA) in Europe, and NA (95% CI, 5.3–NA) in Nagoya (P = .15) (Fig. 2a). Median PFS of patients with invasive carcinoma was NA (96% CI, 2.2–NA) in Europe, and 7.1 years (95% CI, 4.8–NA) in Nagoya (P = .35) (Fig. 2b). Similarly, no differences in median PFS were observed in patients with non-invasive disease (i.e., low-grade dysplasia, adenoma or carcinoma in situ) between both regions (Fig. 2c).




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**Table 4** Pathology report

| | Europe, n = 85 | Nagoya, n = 91 | P value |
|---|---|---|---|
| Localization of the lesion(s), n (%) | | | |
| Intrahepatic | 44 (51.8) | 22 (24.2) | <.001 |
| Extrahepatic above cystic duct | 27 (31.8) | 39 (42.9) | .17 |
| Extrahepatic below cystic duct | 31 (36.5) | 33 (36.3) | 1.0 |
| Number of lesions, n (%) | | | <.001 |
| Single | 65 (76.5) | 89 (97.8) | |
| Multiple | 20 (23.5) | 2 (2.2) | |
| Diameter of largest lesion, mm, median (IQR) | 20 (15–33) | 20 (15–30) | .85 |
| Presence of mucin, n (%) | 27 (31.8) | 32 (35.2) | .75 |
| Degree of atypia, n (%) | | | <.001 |
| Low-grade dysplasia/adenoma | 24 (28.2) | 0 | |
| High-grade dysplasia/carcinoma in situ | 25 (29.4) | 14 (15.4) | |
| Invasive carcinoma | 36 (42.4) | 77 (84.6) | |
| Invasion, n, yes/no/unknown | | | |
| Stromal | 16/59/10 | 49/42/0 | |
| Vascular | 9/69/7 | 15/76/0 | |
| Lymphatic | 9/64/12 | 23/68/0 | |
| Perineural | 13/62/10 | 31/60/0 | |
| Resection margin status, n (%) | | | .96 |
| R0 | 69 (81.2) | 75 (82.4) | |
| R1 | 14 (16.5) | 15 (16.5) | |
| R2 | 1 (1.2) | 1 (1.1) | |
| Unknown | 1 (1.2) | 0 | |
| Lymph nodes harvested | | | |
| Patients, n (%) | 61 (71.8) | 88 (90.1) | <.001 |
| Number, median (IQR) | 6 (2–16) | 11 (7–18) | .009 |
| Lymph nodes positive | | | |
| Patients, n (%)[a] | 11/47 (23.4) | 13/91 (14.3) | .27 |
| Number, median (IQR) | 3 (2–4) | 2 (1–3) | .21 |

[a] Two of 11 patients with positive lymph nodes in the European cohort, and one of 13 patients with positive lymph nodes in the Japanese cohort had carcinoma in situ. The rates of nodal metastases were calculated by taking as denominator the sum of patients with carcinoma in situ and patients with invasive carcinoma.

## Discussion

This international study compared two series of patients with IPNB, a rare disease worldwide. Pathologic, perioperative and survival outcomes were compared in two geographic regions of the world with different disease prevalence and distinctive genetic and environmental risk factors. Demographic differences between European and Japanese patients were significant. Median age of European patients was within the range described by the WHO (50–70 years), whereas Japanese patients were typically older.[1] There was gender parity in Europe, whereas the proportion of males affected by IPNB was higher in Nagoya. All Japanese patients were of Asian descent, whereas 13% of Europeans were non-Caucasian of Asian, African or Latin descent. A noteworthy difference was also observed in body weight, with European patients having a higher BMI compared to their Japanese counterparts.

Jaundice was present as an initial symptom in 33% of 391 patients with IPNB, according to a systematic review including 10 studies worldwide. In the present series, only 18 (23.4%) of the 77 Japanese patients with invasive carcinoma had jaundice at onset. IPNB is frequently diagnosed at an early stage in Japan, possibly owing to the regular health screenings conducted in the country. This proactive approach enables the asymptomatic identification of tumors, resulting in a lower incidence of jaundice as a presenting symptom. Furthermore, jaundice is less frequently observed in papillary tumors like IPNB as compared to non-papillary tumors. This phenomenon can likely be attributed to the inherent soft texture of intraluminal papillary tumors in contrast to the infiltrative




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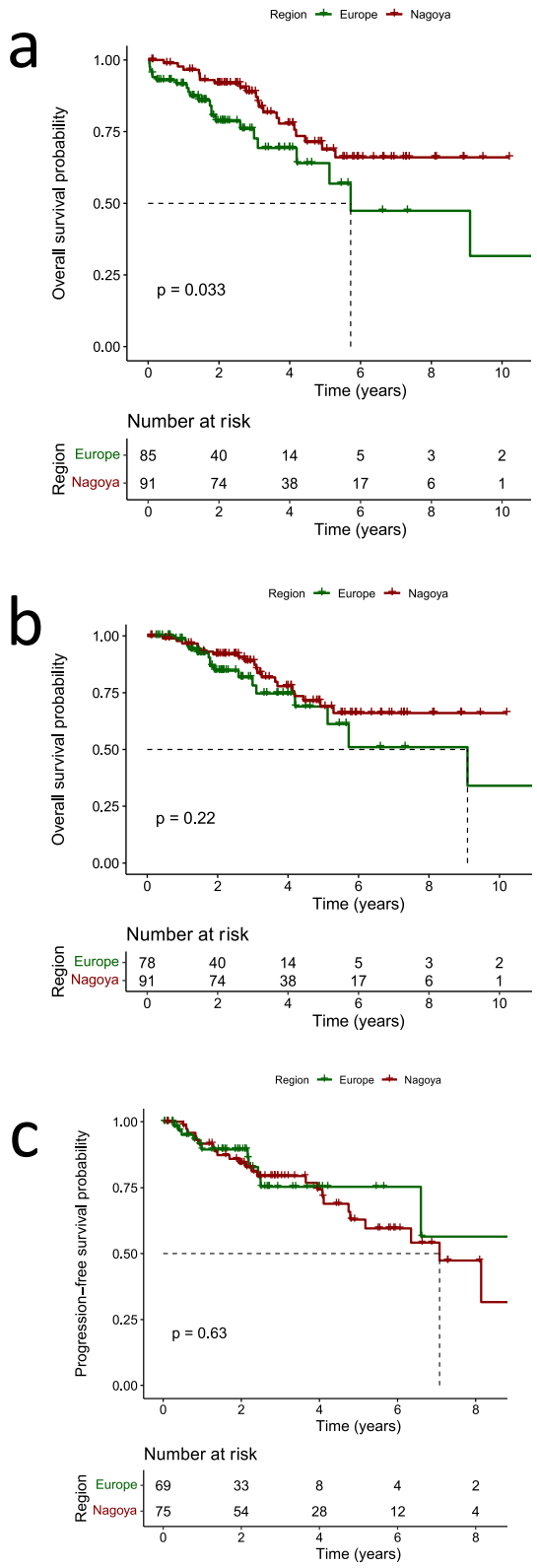


nature of non-papillary neoplasias. Risk factors such as hepatolithiasis and clonorchiasis, which are commonly linked to IPNB in Eastern Asian countries, were not present in any of the Japanese patients, and were only present in two European patients.[1]

A minimally invasive approach was performed only in a minority of cases in Europe. The surgical protocol in Nagoya consisted of more extensive resections which included bile duct excision and lymph node dissection for the majority patients. As a result, operative times were longer, intraoperative blood loss was higher, and there was a greater likelihood of requiring blood transfusion. Additionally, median length of hospital stays (28 days vs 11 days), Clavien–Dindo grade $\geq$3 complications (68% vs 33%), postoperative liver failure (21% vs 8%), and postoperative pancreatic fistula (40% vs 15%) were significantly higher in Nagoya. On the other hand, 90-day readmission (3% vs 20%) and 90-day reoperation (2% vs 14%) rates were higher in Europe.

Recently, a new classification system has been proposed that distinguishes IPNB tumors into type 1 and type 2, based on their similarity to their counterparts in the pancreas (i.e., IPMN).[1] IPNB type 1 is less aggressive and often grows in intrahepatic bile ducts. On the other hand, IPNB type 2 is more prone to invasive carcinoma, commonly found in extrahepatic bile ducts, and results in poorer postoperative outcomes.[1] Our study recruited patients operated on between 2010 and 2020, prior to the updated WHO classification, and was therefore unable to categorize tumors according to this system. Additionally, more intrahepatic tumors, and fewer invasive carcinomas were found in Europe. Based on the available data, it is possible to speculate that tumors in Nagoya exhibit a more invasive behavior.

The oncogenic development of IPNB progresses in a stepwise manner, from low-grade dysplasia to invasive carcinoma.[1,6,35] According to a systematic review, 45% of IPNB tumors showed dysplasia or adenoma, while 55% displayed carcinoma in situ or invasive carcinoma.[36] In Europe, over 40% of patients presented with low- or high-grade dysplasia, whereas no patients in Nagoya exhibited evidence of early-stage tumor progression. These findings suggest that the two cohorts might potentially have different evolutionary profiles.

To our knowledge, long-term outcomes of surgically resected IPNBs in Western countries have been previously reported in only two studies. A single-center study including 39 patients from the US found a 5-year OS of 50%, while a European multicenter study with 45 patients reported a 3-year OS of 76%.[5,6] On the other hand, six studies from single centers in East

**Figure 1** a) Overall survival of all patients; b) overall survival excluding patients who died within 90 days postoperatively; c) progression-free survival of patients with an R0 margin




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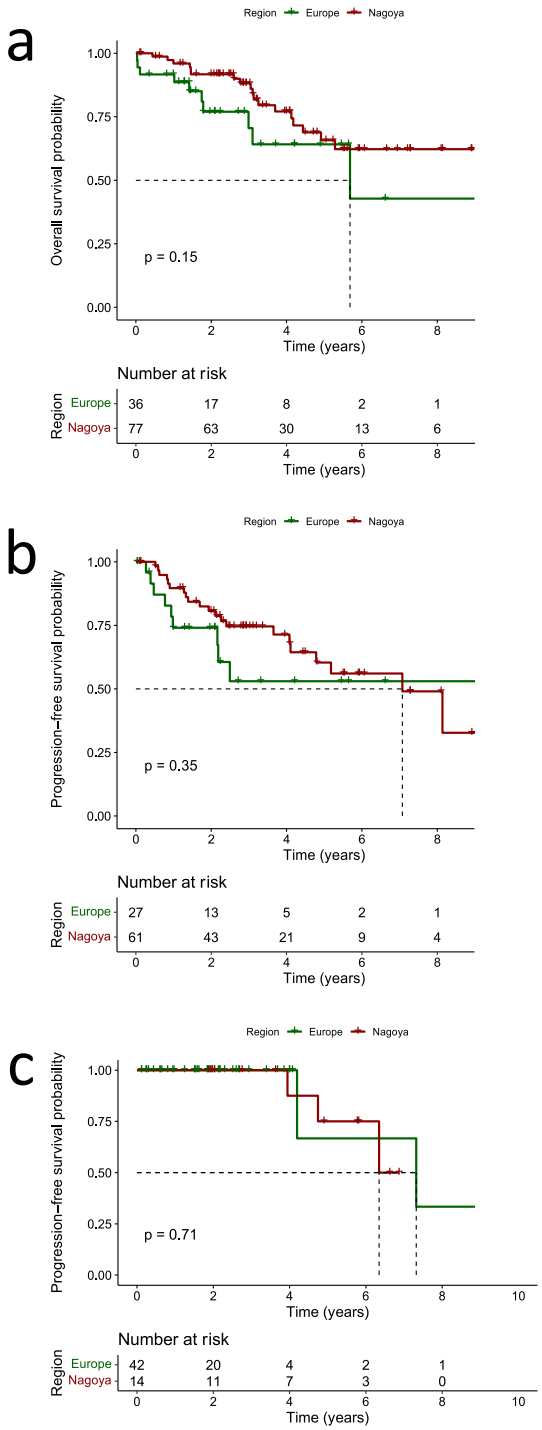


**Figure 2** a) Overall survival of patients with invasive carcinoma; b) progression-free survival of patients with invasive carcinoma and an R0 resection; c) progression-free survival of patients with non-invasive disease (i.e., low-grade dysplasia, adenoma, carcinoma in situ)

Asia showed a pooled 5-year OS of 64% (49–77.3).[10–12,14,15,19] If calculated from the date of surgery, the present study found a 5-year OS of 63% (95% CI 50–82) in Europe, and 69% (95% CI 58–82) in Nagoya, which are within the range described in the previous reports. In our current comparative study, we observed that Japanese IPNB patients had fewer associated comorbidities, as measured by ASA score and ECOG performance status, than European patients. Furthermore, Europe exhibited an elevated rate of postoperative morbidity within the 90-day timeframe. This discrepancy can be elucidated by the increased volume of cases handled and the methodological approach to surgical resection adopted by a singularly dedicated HPB team based in Nagoya. Excluding 90-day postoperative deaths, oncological outcome after IPNB resection was similar between both regions.

Tumor multiplicity has been described to be an independent prognostic factor of poor OS and PFS in patients with IPNB. A study from Korea including 84 patients found that 5-year OS (85.9% vs 50.7%) and 5-year PFS (74.1% vs 36.1%) were better in patients with single than multiple tumors.[9] Similarly, another study from the same country including 120 patients reported better 5-year PFS (85.1 vs 46.9%) in patients with a single tumor than multiple lesions.[16] In our previous European study we also described better 5-year OS in patients with solitary lesions.[7]

On the other hand, a single-center study conducted in Japan, which included 21 patients, demonstrated that those with intrahepatic tumors had significantly better 5-year OS rates (81.8% vs 45%) and 5-year PFS rates (81.8% vs 16.2%) compared to those with extrahepatic tumors.[17] Similarly, our European cohort study also revealed that patients with intrahepatic lesions had better 5-year OS than those with extrahepatic tumors.[7] However, mortality outcomes cannot be solely attributed to the tumor location, as the proportion of patients with intrahepatic tumors was lower in Nagoya compared to Europe.

Three studies from East Asia reported 5-year OS rate of 79% (76–81) in a subgroup of patients with invasive carcinoma.[15,21,22] In our study, 5-year OS rate of patients with invasive carcinoma was similar in both regions and slightly poorer than in the above studies.

A limited number of studies from East Asia reported on PFS based on subgroups of patients (i.e., intra vs extrahepatic, type 1 vs type 2, single vs multiple tumor).[9,16–18] The current study found no significant differences in PFS in both cohorts, nor in the subgroup of patients with invasive carcinoma. Patients who experienced disease recurrence received similar salvage or palliative treatment strategies in both regions.

Apart from its retrospective design, the main weakness of this study was the inclusion of patients from a multicenter cohort in Europe and from a single center in Nagoya. However, data collection using a single shared extraction form through a common capture platform for both cohorts seemed a feasible way




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to compare variables and outcomes consistently. The effort made by the Nagoya group to adapt their data collection to the requirements of the extraction form is to be commended. This study was only a novel first step to bring together two scenarios of a rare disease in two geographical regions of the world. The purpose was to learn new therapeutic approaches that would serve to develop quality improvement strategies in Western countries, where fewer cases of this disease are diagnosed. A second weakness was not segregating IPNB into types 1 and 2 according to the most recent 2019 WHO tumor classification. This initiative would have been feasible in Nagoya but extremely difficult to carry out retrospectively in Europe. Including the new classification in the evaluation of new patients with IPNB in Western countries is highly recommended. This updated approach can help enhance the accuracy of disease staging and improve patient outcomes. The revision of the pathology slides by the same pathologist applying uniform diagnostic criteria was initially considered to enhance the quality of the study. Unfortunately, this strategy was not feasible with the available resources since the study included patients operated on between 2010 and 2020 retrospectively collected from multiple institutions. Additionally, the experience of pathologists from European centers was presumably limited due to the low volume of patients treated with this disease. Therefore, a decision was made to consider the pathological diagnosis made by each local pathologist, acknowledging this limitation while interpreting the results. For the reasons described above, T stage was categorized using intra-, perihilar, and extra-hepatic definitions. Therefore, data regarding the T stage has not been provided. Unfortunately, the degree of dysplasia of positive resection margins was not recorded separately.

## Conclusions

This first comparative analysis of patients with IPNB from Europe and Japan highlights differences in demographic factors, underlying health conditions, tumor characteristics, and surgical management between both regions. Despite performing more extensive resections, the low perioperative mortality observed in Nagoya is likely attributed to a combination of patient-, tumor-, and surgery-related factors and to the expertise in the management of these patients in Japan. Excluding 90-day postoperative deaths, survival was similar in both regions. The wealth of experience gathered by Asian centers could serve as a valuable reference for potentially advancing the treatment of IPNB patients, refining management strategies, and enhancing patient outcomes in Western countries.

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### Data availability statement

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

### Conflicts of interest

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

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2024.01.009.




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