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Outcome Determining Factors of Intraductal Papillary Neoplasm of the Biliary Tract (IPNB)—a Single Center Survey and Analysis of Current Literature

Philipp Höhn[1] · Chris Braumann[1] · Johanna Munding[2] · Andrea Tannapfel[2] · Waldemar Uhl[1] · Beat M. Künzli[1]

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Abstract

Purpose Intraductal papillary neoplasms of the biliary tract (IPNB) are rare tumors originating from the bile duct epithelium. Metastatic disease of IPNB is extremely rare and only reported in a small number of cases worldwide. Due to this limitation in number, the treatment of IPNB mainly relies on retrospective case series.

Patients and Methods We reported three cases of IPNB, one benign, one carcinoma with lymph node metastasis, and one case with histologically proven metachronous pulmonary metastasis. We correlated our findings with the existing data found in the literature. All patients underwent hemihepatectomy and complete tumor resection was achieved.

Results Diagnosis of IPNB can be challenging due to varying presentation. The treatment of choice is surgical oncological resection in an early tumor stage. Long-term outcome highly depends on the underlying grade of dysplasia, multiplicity, and tumor-free margins. Aggressive tumor invasion is reported in up to 72% of cases in IPNB. Furthermore, the recurrence rate of IPNB is high with up to 22%. Further factors associated with an impaired survival are incomplete resection, lymph node involvement, and MUC1 expression.

Conclusion High potential for dysplasia and proof of invasive carcinoma upon diagnosis are hallmarks of IPNB. Metastatic disease in IPNB is reported only in small numbers. IPNB is an aggressive tumor entity with impaired long-term outcomes. A drawback for interpretation of current data is the fact that they rely on case series and reports and are not validated through more powerful randomized multicentric trials.

Keywords IPNB · Hepatobiliary · Liver cancer · Surgery

Introduction

Intraductal papillary neoplasms of the biliary tract (IPNB) are rare tumors originating from the bile duct epithelium. IPNB display a heterogeneous histopathology and are regarded as biliary counterpart to intraductal papillary neoplasm of the pancreas (IPMN). [1] High potential for dysplasia and proof of invasive carcinoma upon diagnosis are hallmarks of IPNB. Recommendations for management of IPNB currently rely on retrospective case series due to its rare incidence. The occurrence of metastatic disease of IPNB is rare, and only few cases with distant metastatic disease have been reported worldwide. [2] The treatment of choice is surgical oncological resection whenever tumors fulfill the criteria of resectability. Long-term survival and prognosis are highly varied and depend on numerous factors. Multiple studies regarding this topic were recently published and are not included in former meta-analysis [3].

In this article, we aim to demonstrate the wide spectrum of clinical manifestations in IPNB and to provide a comparative analysis of the currently available data on their outcome. We do this by presenting three selected cases which cover the spectrum from benign lesions to the extremely rare case of histologically confirmed metachronous pulmonary metastasis in a Caucasian patient. This case series is accompanied by an in-depth comparison of the available clinical data, focusing on recent outcome and specific articles.

✉ Beat M. Künzli
beat_kuenzli@hotmail.com

[1] Department of Surgery, St. Josef-Hospital, Ruhr-University, Gudrunstrasse 56, 44791 Bochum, Germany

[2] Department of Pathology, Ruhr-University, Bochum, Germany

Case 1, Benign IPNB Lesion

A 71-year-old female Caucasian was deferred to our clinic. She complained about epigastric pain unrelated to diet or body position. Symptoms started about 2 weeks before presentation. Furthermore, weight loss of 6 kg and fatigue were reported. Within the last 12 months (mo) she underwent upper and lower endoscopy without significant pathological findings. Drug history included recently stopped cigarette smoking with approx. 45 packet-years (py). Physical examination revealed an epigastric pressure pain without abdominal tenderness.

Laboratory parameters revealed pathologic parameters as demonstrated in Table 1 at admission: white blood cell count (WBC) 10.067/μl (4600–9500), c-reactive protein (CRP) 213 mg/l (< 5), bilirubin 1.3 mg/dl (< 1.2), creatinine 1.03 mg/dl (0.5–0.9), cancer antigen (CA) 19-9 98.1 U/ml (< 27). Serologic testing for viral hepatitis was negative. Antimitochondrial antibodies (AMA), antibodies to nuclei (ANA), and smooth muscle (ASMA) showed no significant elevation.

Liver function evaluation via noninvasive measurement of indocyanine green elimination (LiMON) test indicated a reduced liver function (PDR 29.3%/min R 15 1.2%). CT scan showed a significant left side cholestasis. Magnetic resonance cholangiopancreatography (MRCP) revealed a highly obstructed left hepatic duct associated with intrahepatic cholestasis in the left liver, strongly suspicious of an obstructive tumor. Further findings included uncomplicated liver and kidney cysts (Fig. 1a).

We initiated an antibiotic treatment with imipenem, which leads to a fast improvement of the patient's condition. WBC and CRP are also normalized quickly. Endoscopic retrograde cholangiography (ERC) was performed including brush cytology. Histopathological examination showed epithelial cells and signs of inflammation. ERC also detected a complete separation of the common bile duct (CBD) and the pancreatic duct with the CBD opening into a separate proximal orifice. Placement of a long plastic stent (15 cm, 10 French) in the left hepatic duct was performed. Follow-up examination via ultrasound confirmed regressive cholestasis. We suspected a cholangiocarcinoma leading to cholestasis by bile duct obstruction and therefore performed a left sided hemihepatectomy and cholecystectomy. Histopathological examination revealed an IPNB of 6.2 × 3 × 2.1 cm^3 volume with low- and high-grade intraepithelial neoplasia, but without malignancy. It contained features of the gastric and pancreatobiliary subtype (Fig. 1b, c, and d). The patient suffered from postoperative small bowl atony and mild dyspnea which could be resolved by conservative treatment. She was discharged on the 19th postoperative day. Following the recommendations of our multidisciplinary cancer conference (MCC) we scheduled a follow-up examination via computer tomography (CT) scan and MRCP.

Table 1 Laboratory parameters on admission

	Patient 1	Patient 2	Patient 3	Range
WBC (/μl)	10,067	4420	normal	4600–9500
LDH (U/l)	normal	224	normal	135–214
GGT (U/l)	normal	136	136	6–42
AP (U/l)	normal	normal	120	35–104
bilirubin (mg/dl)	1.3	normal	normal	< 1.2
creatinine (mg/dl)	1.03	normal	normal	0.5-0.9
uric acid (mg/dl)	normal	7.8	normal	17–49
cholesterin (mg/dl)	normal	252	normal	< 200
CRP (mg/l)	213	8.3	normal	< 5
CA 19-9 (U/ml)	98.1	41.94	61	< 27
AFP (ng/ml)	normal	7.99	9.18	< 7

Case 2, IPNB Carcinoma with Lymph Node Involvement

A 69-year-old Caucasian female presented with elevated liver enzymes and a history of known in size progressing asymptomatic liver cysts. Her medical history included rheumatoid arthritis, obstructive sleep apnea syndrome (OSAS), and post coronary angiography due to transient ischemic heart attack. The following laboratory parameters indicated pathological values as presented in Table 1 at the time of admission (reference values are indicated in parentheses): WBC 4420/μl (4600–9500), lactate dehydrogenase (LDH) 224 U/l (135–214), gamma-glutamyl transpeptidase (GGT) 136 U/l (6–42), uric acid 7.8 mg/dl (17–49), cholesterin 252 mg/dl (< 200), CRP 8.3 mg/l (< 5), CA 19-9 41.94 U/ml (< 27), and alpha-fetoprotein (AFP) 7.99 ng/ml (< 7).

Liver function was evaluated via LiMON method, where normal values for liver function were measured (R 15 4.4%, PDR 20.8%/min).

In CT scan pathological bile duct dilation in liver segment 2 and 3 was reported. MRCP showed a prestenotic bile duct diameter of 3 cm proximal to the common hepatic duct, apart from regular uncomplicated liver cysts of the right lobe. Radiological findings were highly suspicious of a cholangiocarcinoma (Fig. 2a).

The surgical procedure consisted of a left hemihepatectomy and cholecystectomy. Resection margins were based upon intraoperative ultrasound (IOUS) and intraoperative fresh frozen section examination. Histopathological findings revealed an intraductal papillary neoplasm of the liver (IPNB) with high-grade intraepithelial neoplasia and an intermediate-grade adenocarcinoma (G2) of 1.5 × 1 × 0.9 cm in diameter. Examination of the hilar liver lymph nodes revealed a

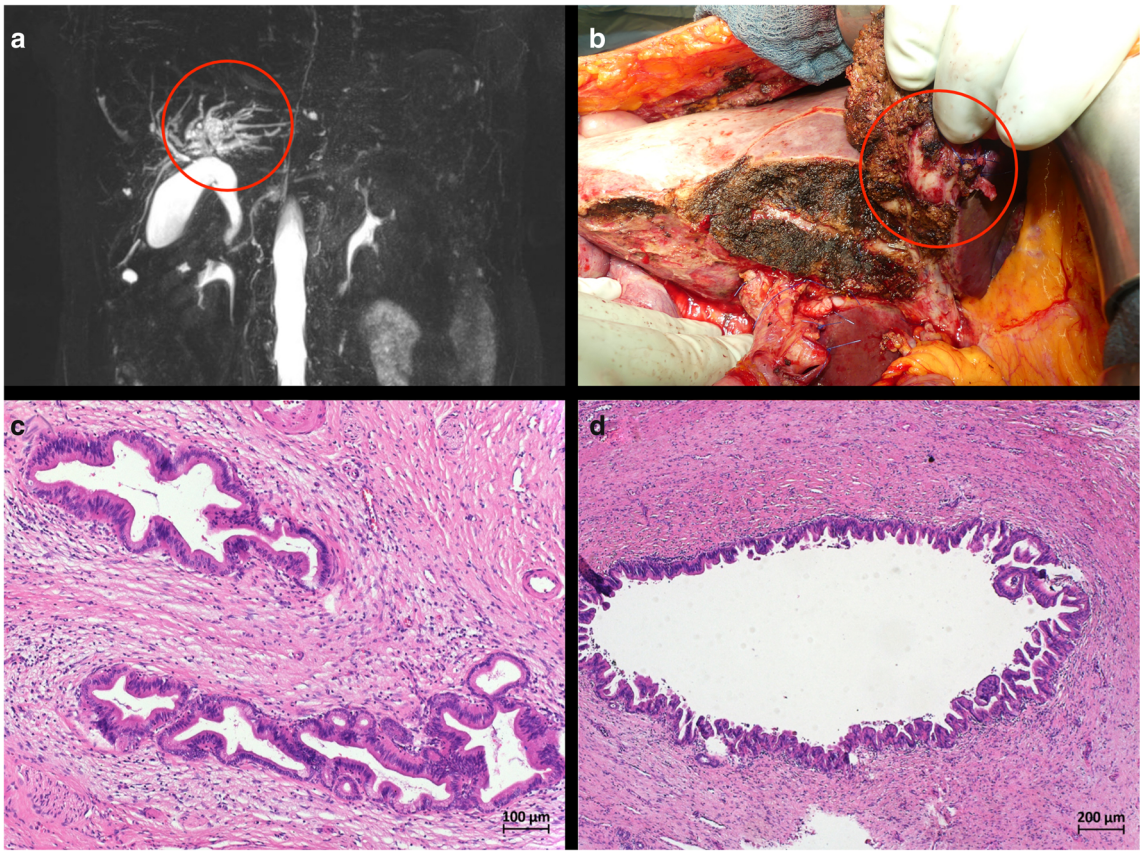

Fig. 1 Radiological, macroscopic, and microscopic findings of patient 1. **a** MRI scan showing pathological left sided bile duct dilation due to an obstruction (red circle). **b** Intraoperative findings of an atrophic left hepatic lobe with the tumor indicated by a red circle. **c** and **d** Microscopic view of IPNB including low- and high-grade intraepithelial neoplasia at different magnification levels. It contained features of the gastric and pancreatobiliary subtype (mix type IPNB)

singular lymph node metastasis. According to these findings, the TNM classification was determined as: pT1 pN1 M0 L0 V0 Pn1, UICC I, and R0 resection (Fig. 2b and c). Postoperative clinical course was uneventful and the patient got discharged at postoperative day 16. Follow-up period of 24 mo postoperatively showed no sign of tumor recurrence. Following the recommendations of the executive medical board after presenting the patient's case at the MCC, adjuvant chemotherapy with gemcitabine was recommended.

Case 3, IPNB Carcinoma with Metachronous Lung Metastasis

The third patient was a 65-year-old female Caucasian. She was referred to our hospital for further evaluation of size-progressive liver cysts. Her medical history was otherwise uneventful. On admission she had no complaints, and physical examination revealed no pathological findings.

Pathological values are presented in Table 1. On admission laboratory findings consisted of: GGT 136 U/l (6–42), alkaline phosphatase (AP) 120 U/l (35–104), CA19–9 61 U/ml (< 27), and AFP 9.18 ng/ml (< 7).

Liver function test via LiMON presented normal values (PDR 23.1%/min R 15 3.1%).

Presence of a colon carcinoma was ruled out by preoperative colonoscopy.

MRCP showed progressive septated liver cysts and dilated bile ducts in the right lobe. Uncomplicated liver cysts were found in liver segment 2, 3, and 4b. The common bile duct (CBD) presented only slightly dilated (10 mm). The expanding liver cysts slightly displaced the right kidney without impaired kidney function (Fig. 3a). CT scan revealed no further pathological findings. We performed an extended resection of the right liver including cholecystectomy using intraoperative ultrasound to determine the extent of resection.

Histopathological findings revealed multiple liver cysts in the right liver lobe. Cysts of 4.5 × 4.3 × 4 cm included a multifocal IPNB associated with high-grade intraepithelial neoplasia and an intermediate-grade adenocarcinoma (G2) with multiple tumor formations (Fig. 3b). Histopathological tumor stage was: pT2 N0 (0/3) M0 V0

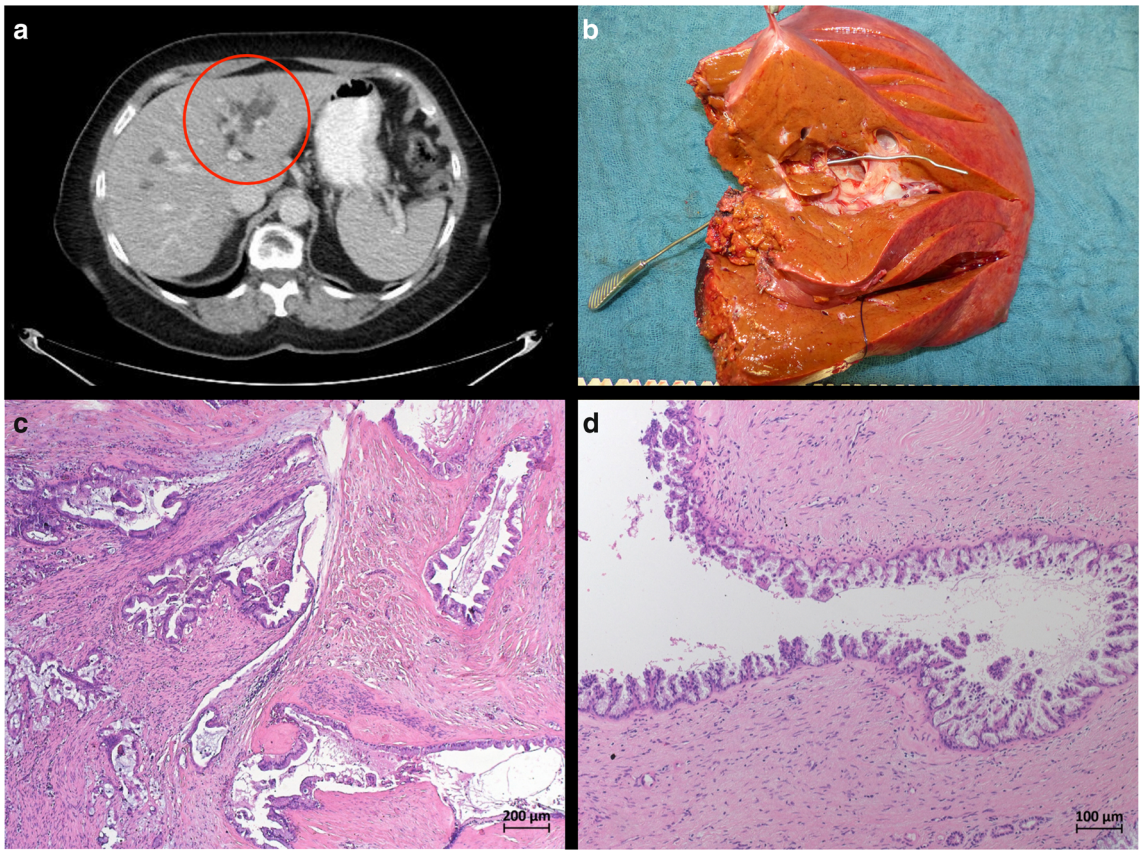

Fig. 2 Radiological, macroscopic and microscopic findings of patient 2. **a** CT scan showing pathological bile duct dilation in liver segment 2 and 3, highly suspicious of cholangiocarcinoma (red circle). **b** Left hemihepatectomy. The specimen was prepared on a BackTable. The metal probe is inserted in the left bile duct and exits through the lesion. **c** and **d** Microscopic view of patient's IPNB associated with high-grade intraepithelial neoplasia (pancreatobiliary subtype) and an intermediate-grade adenocarcinoma at different magnification levels

Pn0, UICC II, and R0 resection. Histopathological findings are displayed in Fig. 3c and d.

MCC recommended adjuvant chemotherapy with capecitabine or gemcitabine.

We discharged the patient on the 17th postoperative day in good clinical condition. Two weeks after being discharged, the patient presented with epigastric pain and fever and had to undergo a CT guided puncture of a 5 × 9 × 4 cm subdiaphragmal bilioma and calculated antibiotic treatment with imipenem. Clinical condition improved within days but continuous biliary secretion had to be treated by ERC placed common bile duct (CBD) stent. Thereafter she recovered uneventful within 6 weeks after surgery with no further treatment needed. Nine months after surgery, the patient developed a suspect pulmonary nodule of the right upper lobe. **(**Fig. 4a**)** Transcutaneous lung biopsy revealed a pulmonary metastasis of the previously resected IPNB. Diagnosis was secured by positive immunohistochemistry for cytokeratin (CK) 7. Napsin A and thyroid transcription factor 1 were not expressed. (Fig. 4b, c, and d) A palliative chemotherapy was initiated following the FOLFOX protocol (oxaliplatin, folic acid, and 5-fluoruracil).

Retrospective Data on Outcome and Prognosis of IPNB

IPNB are defined as singular or multiple macroscopic lesions along the biliary tract with intraluminal growth, prominent papillary proliferation of dysplastic epithelium including frequent intestinal metaplasia, and a variable amount of mucin secretion. Mucin secretion with intraductal tumor growth induces consecutive retention and leads to dilation of the prior duct segments. In contrast to cystic mucinous tumors, they show biliary tract communication and no ovarian-like stroma (OLS) is found. Initially described as a variation of cholangiocarcinoma (CC), they have been recognized by the World Health Organization (WHO) as a distinct pathology in 2010 [4, 5].

IPNB have been described as a biliary counterpart to the intraductal papillary mucinous neoplasms of the pancreas (IPMN) with varying degrees of histopathological similarity. In analogy to IPMN, IPNB are classified into pancreatobiliary, oncocytic, gastric, and intestinal subtypes according to their phenotypical and immunohistochemical features. Tumors presenting characteristics of more than one subtype are not

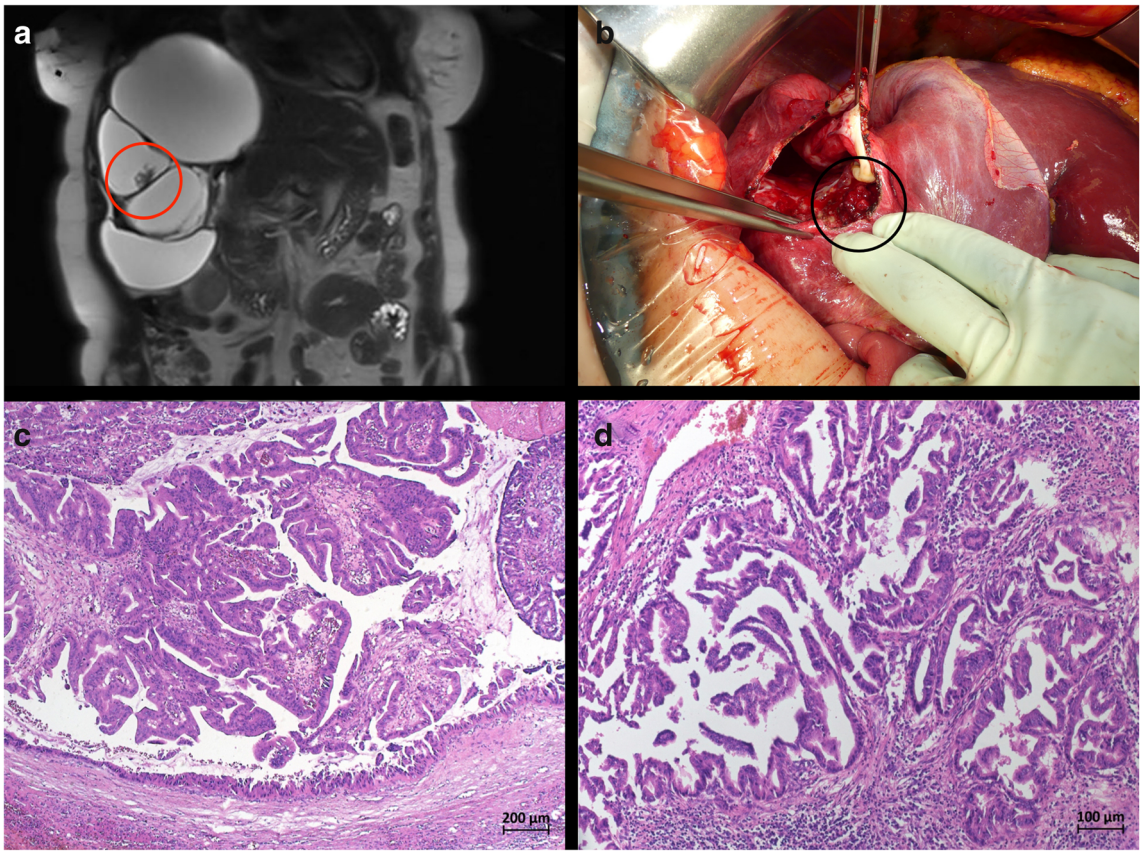

Fig. 3 Radiological, macroscopic, and microscopic findings of patient 3 upon diagnosis. **a** MRI scan showing massive liver cysts of the right lobe, displacing the right kidney. A wall adherent mass can easily be identified (red circle). **b** Intraoperative picture of the wall adherent mass (black circle) after cyst deroofing. **c** and **d** Microscopic view of IPNB associated with high-grade intraepithelial neoplasia (pancreatobiliary subtype) and an intermediate-grade adenocarcinoma at different magnification levels

infrequent. In these cases, the predominant subtype is used for classification [6, 7].

As pulmonary metastasis in IPNB is an extremely rare occurrence we set out to examine the current literature on the expected survival and prognosis of patients diagnosed with IPNB.

In 2016, Gordon-Weeks et al. performed an extensive meta-analysis on the available data for IPNB. They included a total of 57 studies. Fourteen studies were analyzed regarding outcome and prognosis. The highest number of patients (387) was available for 5-year survival and meta-analysis suggested a survival rate of 61% (CI 46–76%). The authors however stated that "Outcome … was in general not well reported and our analysis was further hampered by the fact that a broad range of outcome measures were used. Survival figures at 3 years and 5 years varied dramatically …. This is indeed a drawback of basing an analysis such as ours on case series alone, where practices are not standardized between centers" [3].

Furthermore, three major retrospective studies, covering almost 200 patients, were not included as they were published later on [8–10]. We therefore saw the need to revisit this particular aspect and provide an updated in-depth analysis of the scientific literature. In accordance with Gordon-Weeks et al., we found the available studies unsuited for a statistical meta-analysis as they are highly heterogeneous.

A MEDLINE search was performed via PubMed (https://www.ncbi.nlm.nih.gov/pubmed) using the following input: (((IPNB[Title/Abstract] OR IPBN[Title/Abstract] OR IPNB[Title/Abstract] OR Intraductal papillary neoplasm [Title/Abstract]) AND (("Survival Analysis"[Mesh]) OR ("Treatment Outcome"[Mesh])) NOT "Case Reports" [Publication Type])). Of all 20 results, full text articles were obtained and their references were manually screened for further relevant publications. This led to five additional articles. Of all obtained articles, six did not contain relevant information regarding outcome or prognosis of IPNB [11–20]. Fifteen studies did not explicitly focus on outcome or survival but nevertheless reported relevant data regarding follow-up period, survival time, and 3- and 5-year survival [5, 9, 10, 21–27]. Table 2 summarizes the available data. Two studies reported 1- and 10-year-survival rates which were not included in our table as no comparable data was available. [5, 8] Four studies explicitly

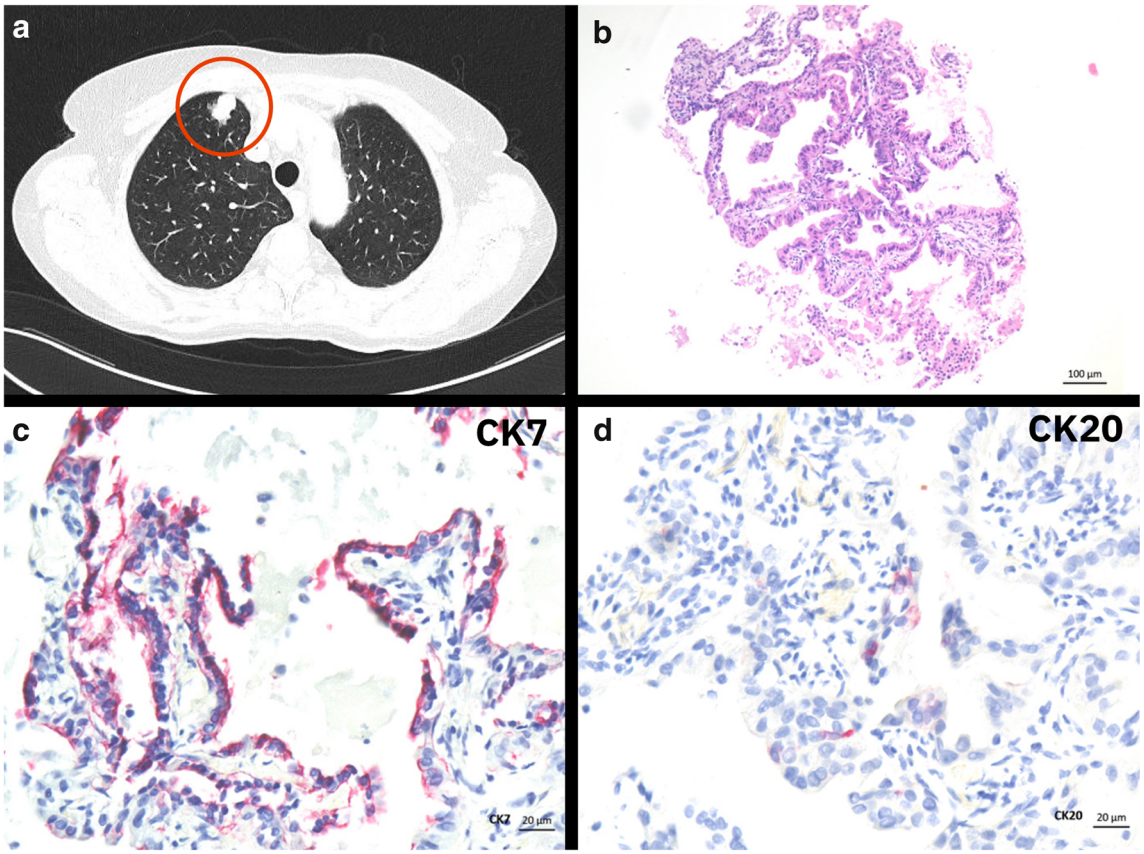

Fig. 4 Radiological and microscopic images of pulmonary metastasis in patient 3. **a** CT scan showing a suspect pulmonary nodule in the right upper lobe of patient 3. **b** Subpleural lung tissue of the upper lobe, including a papillary mucinous neoplasia. **c** Magnified view of same specimen expressing CK7 after immunohistochemical staining. **d** Magnified view of same specimen expressing CK20 after immunohistochemical staining. Expression of Napsin A and TTF1 was negative (not shown)

targeted outcome of IPNB after surgery regarding various variables. [1, 8, 28, 29] The prognostic factors found by these studies are summarized in Table 3.

Rocha et al. performed a retrospective analysis of 343 cases of resected bile duct tumors from 1981 to 2010 in an American population. Thirty-nine (11%) cases of IPNB were identified. Twenty-nine (74%) included an invasive component. Overall median survival was 62 mo for all patients and 49 mo for cases with an invasive component. Median follow-up was 86 mo. R0 resection was associated with an improved median survival (82 mo) compared with R1 resection (36 mo, $p < 0.04$). Patients with a noninvasive carcinoma had a median survival of 144 mo. Depth of invasion beyond 5 mm (39 vs 128 mo, $p < 0.007$) and a percentage of > 10% of invasive cells (42 vs 128 mo, $p < 0.03$) were also associated with a decreased median survival. MUC1 expressing tumors also had a lower survival than MUC1 negative tumors (58 vs 144 mo, $p < 0.009$). In contrast to other studies, resection margins were not significantly associated with survival. Recurrence rate was 37% in case of invasive disease and 20% for initially benign classified tumors after R0 resection [1].

A retrospective analysis of 84 patients undergoing resection of IPNB between 2000 and 2009 was performed by Kang et al. Seventy-five (89%) tumors included invasive components. Median follow-up was 41.8 mo (range, 3.5–123.7). Overall 5-year survival rate for surgically treated IPNB was 64.0%. Median survival was 79.7 mo in these cases. Five-year survival rates were affected by macroscopic morphology (microscopic = 100%, pedunculated = 70%, sessile = 73%, diffuse = 21%; $p = 0.01$). Further prognostic factors included multiple vs. single IPNB (5-year survival rate 50.7 vs. 85.9%; $p = 0.011$) and positive resection margin (5-year survival rate 30% vs. 79.9% after complete resection; $p = 0.010$). Multivariate analysis only revealed that positive resection margin (hazard ratio (HR) 2.523, 95% confidence interval (CI) 1.015–6.274, $p = 0.046$) and multiplicity (HR 2.716, 95% CI 1.055–6.988, $p = 0.038$) were significant negative prognostic factors. Tumor recurrence occurred in 22 (29%) patients and was not influenced by resection margin status. Overall 5-year disease-free survival was 58% after curative resection. Patients with multiple IPNB had a significantly lower survival rate (36.1 vs. 74.1%, $p = 0.026$) [28].

Table 2 Available retrospective data on the outcome of IPNB after resection

Study	Year	No. of patients	Invasiveness			Median follow-up (mo)	Median survival (mo)			3-year survival (%)			5-year survival (%)		
			Be	CiS	Ca		Ov	Be	Ca	Ov	Be	Ca	Ov	Be	Ca
Wu	2018	28	11 (39%)		17 (61%)	29.4 (11.2-47.6)[2]	44.3[2]	55.5[2]	38.3[2]						
Tsai	2013	41	16 (39%)		25 (61%)	5–195	123.5 ± 16.7								
Rocha	2012	39	10 (26%)		29 (74%)	86	62		49						
Paik	2008	25	6 (24%)	1 (4%)	18 (72%)	25.8 (4–59.8)			52.8 (R0)						
Barton	2009	23	4 (17%)		19 (83%)	66			33.6				38% (20–72)[3]		
Luvira	2017	148	24 (16%)	34 (23%)	90 (61%)	44.2	58.6 (47.5–69.7)[3]	102.1 (76.6–127.6)[3]	47.4 (38–56.8)[3]	64				82.1	59.7[5]
Kang	2013	84	9 (11%)		75 (89%)		79.9						64		
Kloek	2011	20	3 (15%)	5 (25%)	12 (60%)	34			50 (11)[1]			67			32
Kubota	2013	119	76 (64%)		43 (36%)					90	85	79	84	85	79
Schlitter	2014	45	31 (69%)		14 (31%)	35 (1–150)				76	77	75			
Choi	2010	55	11 (20%)	6 (11%)	38 (69%)	16 (0–111)				77.6		62.5			
Fujikura	2016	25		13 (52%)	12 (48%)	42 (2–156)[2]							75		
Kim	2011	97	13 (13%)	41 (42%)	43 (44%)	31 (2–119)							83.9–46.8[4]		

mo month, *Ov* Overall, *Be* benign, *CiS* Carcinoma in situ, *Ca* invasive carcinoma

[1] Standard error

[2] mean

[3] 95% confidence interval

[4] dependent on histological subtype (Gastric–Pancreaticobiliary)

[5] after R0 resection

Table 3 Outcome relevant factors in IPNB

	Rocha et al.	Luvira et al.	Jung et al.	Kang et al.
Beneficial factors	Benign IPNB	Benign IPNB	Benign IPNB	
	R0 resection	R0 resection	R0 resection	R0 resection
				Singular IPNB
Nonsignificant factors	Site of IPNB	Site of IPNB	Site of IPNB	
	Resection margin status	Dysplasia at resection margin		
	Epithelial subtype		Epithelial subtype	
	Gender	Gender	Gender	
	Age	Age	Age	
		Lymph node dissection		
				Lymph node involvement
		Serum biomarkers[2]		
	Expression of other MUC proteins[1]			
				Mucin secretion
		Complete caudate lobe resection		
Adverse factors	R1 resection	R1 resection	R1 resection	R1 resection
	Invasive IPNB	Invasive IPNB	Invasive IPNB	
	Lymphovascular invasion	Lymph node involvement	Lymph node involvement	
		Invasive Carcinoma at resection margin	Any dysplasia at resection margin	
	MUC1 expression		MUC1 expression	
	Depth of invasion beyond 5 mm	Level of invasiveness		
	> 10% of invasive cells			
	CEA expression[3]			
				Diffuse morphology

Significant outcome relevant factors in IPNB as found by univariable and/or multivariable analysis in selected studies

[1] MUC2, MUC5AC, MUC6, CDX2, CA125, mesothelin, Ki67, B72.3, HepPar-1, p53

[2] CA19-9, AST, ALT, ALP

[3] in benign IPNB

Another study by Jung et al. retrospectively analyzed 93 IPNB which were surgically resected between 1996 and 2006. Thirty-one (29%) cases included an invasive carcinoma. The authors did not present any numeric survival rates or times. MUC1 expression, lymph node involvement, and the histological status of the resection margin (tumor free vs. dysplasia vs. carcinoma in situ (CiS) vs. invasive carcinoma) were found to be associated with a significantly shorter overall and disease-free survival. Tumors with high MUC1 expression showed a shorter disease-specific and recurrence-free survival compared with low MUC1 expression ($p = 0.0298$) [29].

Luvira et al. did a retrospective analysis of 148 cases of IPNB which were surgically resected between 2005 and 2011 in a single center. They performed an extended analysis on the impact of various factors on overall patient survival after resection. 24 (16%) tumors were adenomas, 34 (23%) CiS, and 90 (61%) invasive carcinomas. Median follow-up was 44 mo and overall median survival time was 58.6 (95% CI 47.5–69.7) mo. Benign tumors had a significantly longer survival (102 mo, 95% CI 76.6–127.6) than malignant IPNB (47.4 mo; CI 38–56.8). Survival was well predicted by level of invasiveness ($p < 0.01$). All patients with completely benign IPNB (adenoma) survived the 5-year postoperative period. In this

study, only the presence of invasive carcinoma at the resection margin was associated with a shorter survival compared with tumor free margins. In case of malignant disease R0 resection was significantly associated with a longer survival (median 63 mo; 95%CI 56–70) vs. non-R0 resection (median 37 mo; 95% CI 23–53) ($p < 0.01$). 5-year survival of patients with malignant IPNB after R0 resection was 60%. It was lower than that of patients who had nonmalignant diseases (5-year survival, 82.1%). Multivariate analysis revealed that lymph node involvement (H 3.94; CI 2.10–7.37; $p < 0.001$) and R1 resection status (HR 1.99; CI 1.17–3.40; $p = 0.011$) were independently associated with a shorter overall survival [8].

Current literature is mainly composed of retrospective studies and case series. This includes the available data on survival and prognosis. Studies report an overall median survival time after resection ranging from 44 to 123 mo [10, 23]. For benign tumors median survival time is increased (55 to 102 mo), compared with IPNB associated carcinoma (33 to 52 mo) [8, 10]. Three-year survival rates can be expected to be at least 60% even in malignant diseases and are generally reported around 80% [5, 8]. Indicated 5-year survival rates range from 38 to 84% regardless of associated carcinoma [22, 24].

Multiple studies have shown that benign IPNB and R0 resection status are independent beneficial factors contributing to the outcome after resection [1, 8, 28, 29]. Recurrence rates of 30% after curative resection of carcinomas are commonly reported [28]. We find it important to point out that even for completely resected benign tumors, recurrence rates of up to 20% have been described [1].

Regarding adverse factors, incomplete resection and presence of invasive components were found to be strongly associated with lower survival in almost all studies [1, 5, 8, 9, 21, 22, 28, 29]. Also majority of studies reported lymph node or lymphovascular involvement to be correlated with a worse outcome [1, 8, 29]. Interestingly even though lymph node involvement was found to be of adverse prognostic influence, none of the studies found a beneficial effect of lymph node dissection [1, 8, 28, 29].

Conclusion

IPNB remain a rare entity of biliary tumors with limited knowledge on optimal diagnosis and management. As case series on Caucasian patients are rare, contributions to this subgroup remain important.

We present a single center experience and case series of three IPNB, which cover the wide-related spectrum of presentation and malign potential. With this case series we hope to extend the clinical knowledge on diagnosis and treatment of IPNB especially in Caucasian patients.

Limited to a small number of cases, the evidence remains weak and conclusions are difficult to make. Only the increase of numbers collected in multicentric randomized trials could bring more evidence-based criteria for treatment and management of IPNB.

Regarding the outcome of IPNB an extensive literature review was performed, and we correlated our findings with current peer-reviewed research.

Compared to, especially branch-type, IPMN most studies covering IPNB report a vastly higher percentage of malignant tumors upon diagnosis. It is also important to notice that recurrence might occur in as much as 20% of patents initially diagnosed with benign tumors.

We therefore strongly suggest a short interval follow-up even on patients with completely resected benign IPNB. Potential hypothesis regarding this fact includes an undetected multilocular occurrence or malignant progression of dysplastic tissue. This is supported by studies finding dysplasia containing resection margins having a critical impact on survival and recurrence. Extra-abdominal metastasis is only found in a minority of tumors and to our knowledge no case of a histologically proven pulmonal metastasis has been reported so far.

Even though the role of lymph node dissection remains controversial, complete oncological resection of the tumor in specialized hospitals is generally highly recommended in the literature. Successful management of patients with tumors developing distant metastasis can be highly challenging even for experienced teams as they are rare and no evidence-based guidelines are available.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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