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REVIEW

Neuroendocrine Tumors of Extrahepatic Biliary Tract

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Abstract Neuroendocrine tumors of the extrahepatic bile ducts (EBNETs) are very rare. The aim of the present review is to elucidate the characteristics of EBNETs, their treatment and prognosis. An exhaustive systematic review of the literature was performed from 1959 up-to-date. One hundred articles, describing 150 cases were collected. Each article was carefully analyzed and a database was created. The most common symptoms were jaundice (60.3 %) and pruritus (19.2 %). Cholelithiasis co-existed in 15 cases (19.2 %). Hormone- and vasoactive peptide- related symptoms were present in only 7 cases (9 %). The most frequent sites were found to be the common hepatic duct and the proximal common bile duct (19.2 %). Surgical management was considered the main treatment for EBNETs, while excision of extrahepatic biliary tree (62.82 %) with portal vein lymphadenectomy (43.6 %) was the most popular procedure. EBNETs are extremely rare. Their rarity makes their characterization particularly difficult. Up to date the final diagnosis is made after surgery by pathology and immunohistochemistry findings. The present analysis of the existing published cases elucidates many aspects of these tumours, giving complete clinicopathological documentation.

Keywords Neuroendocrine tumor · Carcinoid · Biliary neoplasm · Klatskin tumor · Extrahepatic biliary duct obstruction

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Abbreviations

NET	Neuroendocrine tumor
EBNET	Extrahepatic biliary neuroendocrine tumor
WHO	Word health organization
APUD	Amine precursor uptake and decarboxylation
SD	Standard deviation
NSE	Neuron-specific enolase
ERCP	Endoscopic retrograde cholangiopancreatography
VIP	Vasoactive intestinal peptide
CT	Computed tomography
MRI	Magnetic resonance image
VHL	Von Hippel-Lindau syndrome
5-HIAA	5-hydroxyindoleacetic acid
ZES	Zollinger ellison syndrome
PTC	Percutaneous transhepatic cholangiography
G	Grade
HPF	High power fields

Introduction

Carcinoma of the extrahepatic biliary tract accounts for less than 2 % of all cancers. Its commonest type is cholangiocarcinoma accounting for approximately 80 % of the cases, while other types include squamous and adeno-squamous carcinoma, colloid carcinoma, papillary carcinoma, oat cell carcinoma, pleomorphic giant cell tumors and carcinoid tumors [1]. The "carcinoid tumors" have been renamed by the World Health Organization (WHO) [2–4] into "Neuro-Endocrine Tumors (NETs)", in order to designate all gastrointestinal lesions with evidence of endocrine differentiation.

Extrahepatic bile ducts are among the rarest primary sites of NETs, accounting from 0.2 % to 2 % of all such malignancies [3]. These lesions are difficult to be diagnosed

preoperatively and almost impossible to distinguish from cholangiocarcinomas [3, 4].

The aim of the present systematic review article is to elucidate the clinical and pathological features of extrahepatic biliary NETs (EBNETs), their treatment and prognosis by analyzing all published cases.

Material – Methods

In 1959 the first EBNET was reported by Davies [5]. From 1959 up to 2012, 100 articles describing 150 cases were published [5–104]. As EBNET, we describe any NET located on left or right hepatic duct, common hepatic duct, cystic duct or common bile duct. Tumors of the intra-hepatic biliary ducts, liver parenchyma, gallbladder and Vater's region are excluded from this review. Composite tumors including both NET and adenocarcinoma features are excluded as well. Each article was carefully studied and a database was created including the following parameters: age; gender; tumor size and location; presenting symptoms; presence of metastases; time of diagnosis; treatment; immunohistochemistry; pathology and follow up. Immunohistochemistry findings was considered indispensable criterion for inclusion in the database. Cases reporting at least eight characteristics were considered as "well documented".

Results

The majority of the articles (75 %) were published after the 1990's, probably because of the advanced pathological and immunohistochemical techniques which facilitated the diagnosis.

Since we consider by convention that "well documented" is every case that presented minimum 8 characteristics in the database created, 72 cases were excluded from the review as inadequately documented, leaving a total number of 78 "well-documented" cases. Table 1 summarizes all "well-documented" cases with EBNET, while table 2 presents the characteristics of these patients. The female to male ratio was1.6/1 with a mean age of 47.04±17.62 years (ranging from 6 to 79 years). Remarkably, seven cases of EBNETs were reported in children and adolescents [12, 42, 55, 63, 71, 91, 99]. The tumors were symptomatic in 88.5 % of the patients whereas the rest of the cases were incidentally diagnosed either during radiological imaging for other pathology [93] or during operation; usually cholecystectomy [52, 61]. The symptoms were mostly related to the tumor mass growth, invasion of adjacent structures or metastases rather than the hormone and vasoactive peptide secretion. The most common symptom was jaundice (60.3 %), while other symptoms described were abdominal pain (43.6 %), pruritus (19.2 %), nausea-vomiting (12.8 %), weight loss (15.4 %), weakness (5.1 %), anorexia (2.6 %) and fever (2.6 %). Concomitant cholelithiasis was reported in 15 cases (19.2 %). EBNETs rarely induced symptoms associated with hormones or peptides secretion. Only in 7 cases (9 %) presenting symptoms were caused by hormone and vasoactive peptide hyper-secretion; including 4 gastrinomas and 1 somatostatinoma [20, 48, 52, 58, 75, 92]. Diarrhea (7.7 %) and gastrointestinal ulcers (5.1 %) were the most characteristic symptoms caused by hyper-secretion. Though, in only two cases urinary 5-hydroxyindoleacetic acid (5-HIAA) was measured preoperative and found to be slightly elevated [9, 75], gastrin was increased in 3 cases [58, 92] and serotonin in 2 cases [9, 75] respectively. None of the reported hyper-functional EBNETs had liver metastases at the time of diagnosis. Moreover, EBNETs seem to be related to Von Hippel-Lindau syndrome (VHL) in two cases [35, 86], a rare inherited familial cancer syndrome. None of EBNETs cases had clinical features related with carcinoid syndrome.

Regarding the tumor location, the most frequent sites were the common hepatic duct and the distal common bile duct (19.2 %) followed by the middle of the common bile duct (17.9 %), the cystic duct (16.7 %) and the proximal common bile duct (11.5 %). It is noteworthy that the EBNET described by Ueyama et al. [44] arose in a congenital bile duct cyst in common bile duct. Data concerning the tumor size were available in only 68 patients (87.2 %). The mean tumor diameter was 2.15±1.2 cm (ranging from 0.2 to 5.5 cm). It should be noted that very small tumors were found to be more aggressive and having liver metastases [50, 72, 77]. 34.6 % of EBNETs were metastatic either to local lymph nodes (19.23 %) or the liver (16.7 %). In three patients, local invasion of the surrounding structures, such as pancreas or portal vein, was found.

Surgical excision, when feasible, was considered as the main and only curative treatment for EBNETs. The type of procedure depended on the tumor location. The most popular procedure was excision of extrahepatic biliary tree (62.82 %) with portal vein lymphadenectomy (43.6 %). Reconstruction was made mainly by Roux en Y hepaticojejunostomy. Pancreatoduodenectomy was performed for tumors located in the distal common bile duct. Various types of hepatectomies were performed in 11 patients for proximal tumors or liver metastasis. Liver transplantation was performed in 3 patients (3.85 %). In 5 patients the tumors locate on cystic duct and cholecystectomy was considered as adequate treatment. Finally, 4 cases were proved to be inoperable and only biopsies were taken.

EBNETs were difficult to be diagnosed preoperatively. In almost all cases, the final diagnosis was made postoperatively by pathology. In two cases with extensive biliary and liver disease the diagnosis was made in autopsy [12, 39]. Preoperative diagnosis was feasible in only 4 cases (5.12 %). In two patients with biliary mass, serum blood serotonin levels were elevated [9, 75] indicative of functional EBNET. In the other

Table 1 Well-documented extrahepatic biliary neuroendocrine tumors (EBNETs)

Case	Author/Year	Sex/ Age	Location	Size (cm)	Symptoms	Time of diagnosis	Metastasis	Treatment	Immunohistopathology	Follow up (months)
1	Pilz[8]/1961	F/55	CBD	n/a	Weakness	Histology	No	Lap - B	Argentaf +	n/a
2	Little[9]/1968	F/41	PCBD	n/a	Jaundice, pain	Preoperative (elevate urine 5-HIAA level)	Portal vein liver	Lap - B	Argentaf +	Deceased 3 weeks
3	Judge[12]/1976	M/19	LHD	5	Hepatic disease, Ch, pain	Autopsy	Liver, LN	Autopsy	Argentaf +	Deceased 6 day after
4	Schwesinger[13]/1978	F/72	DCBD	2×1.5×1	Jaundice	Histology	No	n/a	Argentaf +	n/a
5	Gerlock[14]/1979	M/32	PCBD	3×4	Jaundice	Biopsy at operation - Histology	No	BDR	Argentaf +	n/a
6	Vitaux[17]/1981	M/30	DCBD	1.5	Jaundice, diarrhea	Histology	LN	PD	Grimelius +	well 48 months
7	Goodman[20]/1984	F/28	CD	n/a	Anorexia, pain	Histology	LN	CH-C, LNR	SS +	Well 9 months
8	Jutte[21]/1986	M/62	CHD	5.5×4×3.5	Pain	Histology	No	BDR, right/left HJ	Grimelius +	Well 24.5 months
9	Gastinger[25]/1987	F/65	PCBD	1	Jaundice, Ch	Histology	Liver	TR	Argentaf +	Well 5 months
10	Reinhardt[28]/1988	F/71	CBD	2.5	Jaundice, pain	Histology	No	PD	Chom +, NSE+	Well 12 months
11	Fujita[29]/1989	F/55	CHD	2	Pain	Histology	No	Choledothotomy, TR, T-tube	Grimelius +	Well 6 months
12	Chittal[30]/1989	F/46	CD	0.8	Pain	Histology	No	Ch-C, partial BDR	Grimelius +, F-M+, cytk +	Well 36 months
13	Van de Wal[32]/1989	M/55	CHD-CD	4	Pain, jaundice	Histology	No	BDR, LNR, HJ Roux en Y	Chrom +	Well 12 months
14	Bumin[34]/1990	F/38	CBD	2	Pain, jaundice, weakness, nausea, vomiting, Ch	Histology	No	Ch-C, choledochotomy, TR, T-tube	Chrom +	n/a
15	Fellows[35]/1990	M/30	PCBD	1.5	VHLS, jaundice, itching	Histology	No	CH-C,BDR, HJ Roux en Y	S-100+, PGP9.5+, cholecystokinin +, gastrin +, Serotonin +	n/a
16	Brown[37]/1990	F/35	CHD - B	2×1×1	Jaundice, pruritus, Ch-C	Histology	No	BDR, LNR, HJ Roux en Y	Chrom +, NSE +, serotonin +, cytk +	n/a
17	B Rodriguez[39]/1991	M/36	CHD - B	3×4	Pain, jaundice, fever, vomiting, pruritus	Histology	liver	Laparotomy	Grimelius +, chrom +, Sph+, NSE+, cytk+	Deceased 4 days after
18	Angeles-A[41, 66]/1991	F/39	CBD	1.5	Pain, jaundice, itching, nausea, vomiting, diarrhea	Histology	No	BDR, LNR, CH-C, Hepaticoduodenal anastomosis	Chrom +, Serotonin +, SS +, Grimelius +	Well 42 months
19	Newman[42]/1992	F/15	DCBD	n/a	Pain, jaundice, weight loss	Histology	No	PPPD	Serotonin +, PP +, glucagone +	Well 48 months
20	Rugge[45]/1992	F/64	CD - CBD	2.5	Jaundice, pain	Histology	No	BDR, LNR, HJ	Chrom +, Ema +, cytk +	Well 12 months
21	Ueyama[44]/1992	F/60	CBD	1.5×1.5	Pain, congenical bile duct cyst	Histology	No	TR, segmenentectomy	Chrom +	n/a
22	Gembala[46]/1993	M/28	RHD - CHD	3	Jaundice, pruritus, weight loss	Histology	No	R- trisegmentectomy, BDR, LNR, left HJ	Chrom +	n/a
23	Sankary[47]/1995	F/47	PCBD	2	I-F	Histology	No	Trisegmentectomy, BDR, HJ Roux en Y	Chrom +	Well 48 months
24	Mandujano[48, 66]/1995	F/53	DCBD	2.2×2	Pain, jaundice, nausea, gastric and duodenum ulcers, Ch	Histology/gastrinoma	No	CH-C, TR	Chrom +, Sph +, Grimelius +, NSE +, gastrin +, PP+, serotonin +	Well 8 months
25	Belli[49]/1996	M/78	PCBD	1.5×0.8×0.6	Jaundice, itching	Histology	No	BDR, LNR, HJ Roux en Y	Chrom +	Well 15 months
26	Kopelman[50]/1996	F/44	CBD	0.5	Jaundice	Histology	liver	Resection of solitary left lobe metastasis - PPPD	Chrom +	Well 18 months
27	Hao[52]/1996	M/42	CBD	1.3×1.1×0.6	I-F	Histology	No	Orthotopic liver transplantation	Chrom +, gastrin +, serotonin +	Well 5 months
28	Meyer[51]/1997	F/56	CD	n/a	Pain	Histology	No	CH-C, CDR	Grimelius +, Chrom +	Well 96 months
29	Shah[54]/1998	F/52	CD	0.5	Pain, nausea	Histology	No	CH-C	Chrom +, NSE+, cytk +	n/a
30	Bembenek[55]/1998	F/12	CHD	1.5	Jaundice, nausea, vomiting, weight loss	Histology	LN	BDR, LNR, HJ Roux en Y	Chrom +, NSE+, cytk +, gastrin +	Well 9 months
31	Ross[59]/1999	F/65	DCBD	2-3	Pain, jaundice, pruritus, diarrhea, weight loss, Ch-C	Histology	LN	PD	Chrom +, NSE +	Well 17 months
32	Perakath[60]/1999	F/36	CHD	n/a	Acute cholangitis	Histology	LN	BDR, HJ	NSE+	Well 6 months

Table 1 (continued)

Case	Author/Year	Sex/ Age	Location	Size (cm)	Symptoms	Time of diagnosis	Metastasis	Treatment	Immunohistopathology	Follow up (months)
33	Hermina[61]/1999	M/69	CD	0.54×0.54X0.1	I-F, Ch-C	Histology	LN	Ch-C, BDR, HJ	Chrom +, Sph+, Grimelius +, PP+	Well 14 months
34	Chamberlain[62, 7]/1999	F/37	CHD - B	2.7×2.4×1.7	Itching	Histology	No	BDR, LNR, HJ Roux en Y	Chrom +, Sph +, PP+	Well 96 months
35	Oikawa[56]/1998	M/70	CD - CBD	2.5×1.5	Jaundice	Histology	Liver	BDR – Liver resection	Chrom +, NSE+, GRP+	Deceased 6 months
36	Martignoti[58]/1999	M/60	CHD	1.3×0.8×0.3	Diarrhea, vomiting, GRD	Histology/gastrinoma	No	TR – T-tube	Chrom +, Sph+	Well 36 months
37	Aronsky[57]/1999	F/64	CD	0.3×0.4	Asymptomatic, gallbladder polyp	Histology	No	Ch-C, BDR, LNR, HJ Roux en Y	Chrom +, Sph+, NSE+, VIP+	Well 47 months
38	Aronsky[57]/1999	F/51	CD	n/a	Ch	Histology	No	Ch-C, BDR, LNR, HJ Roux en Y, liver resection (IV B-V)	Chrom +, Sph+, NSE+, Cytk CAM 5.2+, gastrin +, SS+	Well 49 months
39	Chan[63]/2000	M/14	CHD - B	2.8	Jaundice, pruritus	Histology	No	BDR, LNR, HJ Roux en Y, transhepatic stents	Chrom +, Sph +, serotonin +, VIP +	Well 36 months
40	Juturi[63]/2000	M/43	DCBD	4×3×2.3	Pain, jaundice, nausea, vomiting, weight loss	Histology	LN	PD (Whipple)	Chrom +, gastrin +	Well 42 months
41	Maitra[66]/2000	F/42	CBD	1.1	Jaundice, pruritus	Histology	No	BDR, HJ Roux en Y	Chrom +, SS +	Well 132 months
42	Maitra[66]/2000	F/61	CHD - B	2	Jaundice, pruritus	Histology	No	Ch-C, BDR, HJ Roux en Y	Chrom+, serotonin +	Well 48 months
43	Maitra[66]/2000	F/n/a	CBD	1.4	Pain, jaundice	Histology	LN	BDR, LNR, HJ-Roux en Y	Chrom +, gastrin +	Well 120 months
44	Maitra[66]/2000	F/37	CHD	2.7	Pruritus	Histology	No	Ch-C, BDR, LNR, HJ-Roux en Y	Chrom +, Sph+, PP+	Well 24 months
45	Maitra[66]/2000	F/67	CHD	2.5	I-F	Histology	No	Ch-C, BDR, LNR, HJ-Roux en Y	Chrom +	Well 24 months
46	Turrion[68]/2002	F/51	CHD - B	2.7×1.7×1.5	Jaundice, pruritus, weight loss	Histology	No	Liver transplantation	Chrom +, cytk +, Sph +, 5 % gastrin +, 1 % PP +	Well 18 months
47	Pawlik[69]/2003	M/59	PCBD	1×2	Jaundice	Histology	LN	BDR, HJ	Argentaf +	Well 6 months
48	Pondos[70]/2003	F/65	DCBD	2.2×2×1.7	I-F, Ch	Biopsy during Ch-C	No	BDR, HJ	Chrom +, NSE+	Well 37 months
49	Volpe[71]/2003	M/19	PCBD	1×0.4	Pain, jaundice, Ch	Biopsy during Ch-C	No	BDR, HJ	Chrom +, LMW-cytk +	Well 12 months
50	El Rassi[72]/2004	F/41	LHD - H	4	Jaundice, ulcerous syndrome	Histology	No	Left hepatectomy, LNR, right HJ	Grimelius+, F-M +, Chrom +	Well 240 months
51	El Rassi[72]/2004	M/79	DCBD	0.2	Jaundice	Histology	Liver, LN	PPPD	Grimelius+, F-M +, Chrom +	Deceased 34 months
52	Menezes[73]/2004	M/30	CHD - CD	3	Jaundice	Histology	LN	BDR, LNR, HJ-Roux en Y	NSE +, PGP +	Well 18 months
53	Ligato[74]/2005	F/33	CHD	3.9×2.8×2.6	Irritable bowel syndrome	Histology	No	BDR, LNR, HJ	Chrom +, Sph +, gastrin +	Well 10 months
54	Pithawala[76]/2005	F/38	CBD	5×4×3	Pain, Jaundice, Ch	biopsy during Ch-C	No	BDR, LNR, HJ	Cytk+	Well 2 months
55	Hubert[77]/2005	F/46	CHD - CD	2.5	Pain, jaundice, vomiting	Histology	No	Ch-C, BDR, LNR, HJ-Roux en Y	Chrom +, NSE +, Serotonin+, GRP +	Well 102 months
56	Hubert[77]/2005	M/50	CD	0.4	Pain	biopsy during ERCP	Liver	Ch-C, BDR, LNR, HJ-Roux en Y, RFA for the liver metastasis	Chrom +, NSE +, Sph +	n/a
57	Nesi[75]/2006	M/30	DCBD	1.8×1×0.7	Jaundice, pruritus, weight loss, diarrhea	preoperative (elevate blood serotonin level)	No	PPPD	Chrom +, Sph +, NSE +, cytk +, Serotonin +, Ki-67: 6 %	Well 84 months
58	Tzimas[78]/2006	F/29	LHD	2.8	Jaundice, pruritus, weakness	Histology	Liver (12 months later)	Left hepatectomy+cautade lobe, right HJ/Liver transplantation	Chrom +, Sph +	Well 24 months
59	Kim[79]/2006	F/67	DCBD	1.6×1.5×0.5	Pain, jaundice	Histology	LI	PPPD	Chrom +, Sph +, CD56 +	Well 10 months
60	Caglikulekci[80]/2006	F/40	CBD	0.7	Pain, jaundice, weight loss, Ch	Biopsy during Ch-C	LN, LI	BDR	Chrom +	Deceased 14 months
61	John[82]/2006	F/67	CBD	n/a	Jaundice	Histology	n/a	PD (Whipple)	Chrom +, Sph+, NSE+	n/a
62	Honda[81]/2006	M/76	DCBD	1.4×1	Pain, jaundice	Histology	Liver	PD (Whipple)	Grimelius +, Chrom +, Sph +	Well 8 months
63	Ferrone[6]/2007	M/52	RHD -H	2.2	No symptoms	Histology	No	Right trisegmentectomy, BDR, LNR	Chrom +, Sph +, monoclone CEA -, Ki-67<2 %	n/a
64	Sethi[7]/2007	M/51	PCBD	2.5×2.2×2.8	Leg swelling, weight loss	Histology	No	BDR, LNR, HJ Roux en y	Chrom +, Sph +	Well 22 months
65	Todoroci[83]/2007	M/73	DCBD	1×1.2×0.7	Pain, fever	Histology	No	PPPD	Chrom +, Sph +, NSE +, PP +, Grimelius +	Well 12 months

Table 1 (continued)

Case	Author/Year	Sex/ Age	Location	Size (cm)	Symptoms	Time of diagnosis	Metastasis	Treatment	Immunohistopathology	Follow up (months)
66	Colombo[84, 98]/2007	M/52	CBD	2	Jaundice	Histology	No	BDR, LNR, HJ	Chrom +, Sph +	Well 41 months
67	Stavridi[85]/2008	F/49	CD	1.4	I-F, Ch	Histology	No	Ch-C	Chrom +, Sph +, CD56 +	Well 12 months
68	Nafidi[86]/2008	F/31	CBD	1.2×1	VHLS, pain, jaundice	Histology	No	BDR, LNR, HJ	NSE +	n/a
69	Gusani[88]/2008	F/43	CHD	2.5×1.2×1.1	Jaundice	Histology	No	BDR, LNR, HJ- Roux en Y	Chrom +, Sph +, Grimelius +	Well 132 months
70	Ferekouras[89]/2009	F/60	CD	2.1×1.2×1	Jaundice, nausea, anorexia, weakness, weight loss	Histology	Liver	BDR, LNR, HJ- Roux en Y – stent	Chrom +, Sph +	Well 112 months
71	Price[92]/2009	F/55	CD – CHD	0.6	MEN-1, ZES	Histology/gastrinoma	Liver	Choledochotomy, TR, T tube, LNR, RFA for liver metastasis	Chrom +, gastrin +	Well 24 months
72	Price[92]/2009	F/33	DCBD	n/a	GRD, MEN-1, ZES	Histology/gastrinoma	LN	PPPD	Chrom +, gastrin +	Well 24 months
73	Tonhofer[91]/2009	F/6	CHD	n/a	Jaundice	Histology	No	BDR – LNR - HJ	Chrom +, Sph +, NSE +	Well 24 months
74	Marecki[93]/2009	M/71	CHD - B	1.5×1.6	Ch, pain	Biopsy during ERCP	Liver	Laparotomy - unresectable	Sph +, NSE +, cytk CAM 5.2 +, cytk 7 +	Well 7 months
75	Squillaci[98]/2010	M/70	CHD	4.5×2.6	Pain, Ch	Biopsy during Ch-C	No	Left hepatectomy, BDR, LNR, HJ Roux en Y	Chrom +, Sph +, SS +, PP +	Well 59 months
76	Zhan[99]/2010	M/10	DCBD	2×1.5×1	Jaundice, pain	Histology	No	PD, LNR	Chrom +	Well 12 months
77	Cappell[102]/2011	M/42	DCBD	1.8	Jaundice, pain, weight loss	Histology	No	PD	Chrom +, Sph +	n/a
78	Bhalla[104]/2012	F/28	CHD	2	Pain, weight loss	Histology	LN	BDR, LNR, HJ Roux en Y	Chrom +, Sph +, CDX2 +	Well 4 months

M: Male, *F*: Female, *CBD*: Common bile duct, *CHD*: Common hepatic duct, *RHD*: Right hepatic duct, *LHD*: Left hepatic duct, *CD*: Cystic duct, *PCBD*: Proximal common bile duct, *DCBD*: Distal common bile duct, *CHD-B*: Common hepatic duct bifurcation, *LHD-H*: Left hepatic duct-hilar, *RHD-H*: Right hepatic duct – hilar, *I-F*: Incidental finding, *Ch*: Cholelitiasis, *VHLS*: Von Hippel-Lindau syndrome, *GRD*: Gastrointestinal reflux disease, *MEN-1*: Multiple endocrine neoplasia syndrome type 1, *ZES*: Zollinger – Ellison syndrome, *Ch-C*: Cholecystectomy, *LN*: Lymph nodes, *LI*: Local invasion, *Lap-B*: Laparotomy-biopsy, *TR*: Tumor resection, *PD*: Pancreatoduodenectomy, *PPPD*: Pylorus preseving pancreateduodenectomy, *BDR*: Bile duct resection, *LNR*: Lymph nodes resection, *HJ* – Roux en *Y*: Hepaticojejunostomy Roux en Y, *RFA*: Radio-frequency ablation, *CDR*: Cystic duct resection, *SS*: Somatostatin, *Sph*: Synaptophysin, Chrom: Chromogranin A, *PP*: Pancreatic polypeptide, *Cytk*: Cytokeratine, *F-iM*: Fontana-Masson

Table 2 Extrahepatic biliary neuroendocrine tumors (EBNETs) characteristics

Gender	Male	n: 30	38.5 %
	Female	n: 48	61.5 %
Age (years)	Mean	47.04±17.62	Range: 6 – 79
Tumor size (diameter in cm)	Mean	2.145±1.19	Range: 0.2 – 5.5
Tumor location	RHD	n: 2	2.6 %
	LHD	n: 3	3.8 %
	CHD bifurcation	n: 7	9.0 %
	CHD	n: 15	19.2 %
	CD	n: 13	16.7 %
	PCBD	n: 9	11.5 %
	CBD	n: 14	17.9 %
	DCBD	n: 15	19.2 %
Symptoms	Abdominal pain	n: 34	43.6 %
	Jaundice	n: 47	60.3 %
	Pruritus	n: 15	19.2 %
	Nausea – Vomiting	n: 10	12.8 %
	Cholelithiasis	n: 15	19.2 %
	Weight loss	n: 12	15,4 %
	Incidental finding	n: 8	10.3 %
	Diarrhea	n: 6	7.7 %
	Gastrointestinal ulcers	n: 4	5.1 %
Metastases	No	n: 50	64.9 %
	Liver	n: 13	16.9 %
	Lymph nodes	n: 15	19.48 %
	Local invasion	n: 3	3.9 %
Treatment	Inoperated – biopsy	n: 5	6.41 %
	Local resection	n: 7	8.97 %
	Radical resection	n: 65	84.62 %
	Bile ducts resection - Hepaticojejunostomy	n: 49	62.82 %
	Pancreatoduodenectomy	n: 15	19.23 %
	Hepatectomies/RF ablation	n: 11	14.1 %
	liver transplantation	n: 3	3.85 %
Perioperative mortality		n: 3	3.85 %
Follow up (months)	Mean	35.28±42.3	Range: 1 – 240

EBNETs: Extrahepatic biliary neuroendocrine tumors; *RHD*: Right hepatic duct; *LHD*: Left hepatic duct; *CHD*: Common hepatic duct; *CD*: Cystic duct; *PCBD*: Proximal common bile duct; *CBD*: Common bile duct; *DCBD*: Distal common bile duct; *RF*: Radio frequency

two cases the diagnosis was made by biopsies taken during endoscopic retrograde cholangiopancreatography (ERCP) [77, 93].

Immunohistochemistry was available in all included cases. Table 3 includes the diagnostic neuroendocrine markers expressed by EBNETs. The vasoactive peptides produced by these tumors were gastrin (14.1 %), serotonin (12.8 %), pancreatic polypeptide (10.3 %) and somatostatin (6.4 %). More rarely, the EBNETs stained positive for VIP (2.6 %), gastrin released protein (2.6 %), protein gene product (2.6 %), glucagon (1.3 %) and cholecystokinin (1.3 %). In only 7 cases these peptides were active to cause symptoms and the final diagnosis was well differentiated endocrine tumor [20, 52, 75]; mostly gastrinoma [48, 58, 92]. Three patients (4.1 %), died during the perioperative period. Follow-up surveillance data were available for 60 patients (82.2 %) and ranged from 1 to 240 months.

Discussion

NETs are distinct neoplasms with characteristic histological, clinical and biological properties. NETs consist of multipotential cells with the ability to secrete numerous hormonal substances and vasoactive peptides; serotonin, gastrin, somatostatin, VIP, glucagon and insulin being the most common. The most common sites for primary NETs are the appendix, bronchus, ileum and rectum. NETs was assumed

Table 3 Extrahepatic biliary neuroendocrine tumors (EBNETs) immunohistochemistry

Chromogranin A	n: 59	75.6 %
Synaptophysin	n: 29	37.2 %
Neuron-specific enolase (NSE)	n: 21	26.9 %
Cytokeratines	n: 12	15.4 %
Gastrin	n: 11	14.1 %
Serotonin	n: 10	12.8 %
Pancreatic peptide (PP)	n: 8	10.3 %
Somatostatin	n: 5	6.4 %
Cholecystocinin	n: 1	1.3 %
Glucagone	n: 1	1.3 %
Vasoactive intestinal peptide (VIP)	n: 2	2.6 %
Gastrin release protein (GRP)	n: 2	2.6 %
Protein gene peptide (PGP)	n: 2	2.6 %

to arise from embryonic neural crest cells, which are known as enterochromaffin or Kultschitsky cells that migrate to the respiratory and gastrointestinal tracts during neonatal development [3]. The origin of these cells from neural crest have been recently questioned [105] based on studies such as that by Fontaine and Le Douarin [106]. Kultschitsky cells are extremely scarce in bile duct mucosa, possibly explaining the rarity of EBNETs [88]. According to the analysis of 13,715 NET cases of all organs of the digestive system by Modlin et al. [107], the incidence of EBNETs was 0.32 %.

A multitude of terms has been used to describe EBNETs including "apudoma", "argentaffin tumor", "carcinoid", "malignant carcinoid", "atypical carcinoid", "adenoendocrine carcinoma" and"endocrine cell carcinoma". Carcinoid is the most common term used to describe these tumors before 1996, when WHO initially by Klöppel et al. [108] and subsequently by Capella et al. [4] has agreed to replace it with the broader term "neuroendocrine tumor". It includes all endocrine tumors, ranging from well differentiated (traditionally known as carcinoid tumors) to poorly differentiated malignancies with endocrine features (e.g. small cell carcinoma). WHO's staging system is based on tumor size, number of mitoses per high-power field, vascular or perineural invasion and Ki-67 immunostaning to differentiate between the various grades and potential malignancy of NETs [4]. The WHO recently (2010) revised NETs classification [109]. The new classification emphasize to the NET's grade. Three NETs categories are defined regarding to the grade (G): G1, mitotic index count<2 mitoses per high-power fields (HPF) and/or Ki-67 index< 2 %; G2, mitotic index count 2–20 mitoses per HPF and/or Ki-67 index 3-20 %; G3, mitotic index count>20 mitoses per HPF and/or Ki-67 index>20 %.

The origin of EBNETs remains to be elucidated. Some authors assumed that these neoplasms derive from pre-existing neuroendocrine cells that are physiologically dispersed throughout the biliary mucosa [88]. Another hypothesis was that these tumors originate from ectopic pancreatic tissue distributed during embryogenesis within the biliary ducts [92, 94]. Other authors incriminated a multipotent stem cell of the biliary mucosa, capable of differentiating into NETs and carcinomas [83]. The theory that EBNETs originated from a multipotent stem cell is supported by the mixed phenotypes of EBNETs, ranging from pure EBNETs to composite tumors and to carcinomas with scattered neuroendocrine cells [57]. Chronic inflammation and intestinal metaplasia are implicated in tumor-genesis because NETs are frequently encountered along with these conditions. Chronic inflammatory conditions of the bile ducts result in intestinal metaplasia; as a result an increase in the number of argentaffin cells is observed. This may predispose the ducts to possible EBNET development [37]. In the present review, cholelithiasis associated with EBNETs is found in 19.2 % of the studied cases. The high incidence of cholelithiasis could be associated with EBNETs pathogenesis.

The endocrine nature of EBNETs can't be usually diagnosed preoperatively because of the absence of detectable serum markers and the usual lack of hormonal symptoms [64]. In only two cases urinary 5-hydroxyindoleacetic acid (5-HIAA) was measured and found to be slightly elevated [9, 75]. Preoperative gastrin serum level was increased in 3 cases [58, 92]. Yet, only in Martignogni et al. [58] case preoperative images assisted in localizing the tumor in biliary ducts. Despite the availability, the technological advances and use of many diagnostic imaging tools, preoperative diagnosis is difficult because of the similarity of findings among biliary malignancies. In the vast majority of the cases, the diagnosis is made intra-or postoperatively by pathology reports. Preoperative diagnosis could be made by endoscopic biopsies, but the incidence of false negative results in brush cytology may be high due to submucosal location of the neoplasm. Noronha et al. [94] in her recent review suggested that accurate preoperative diagnosis can be made by examining brush cytology specimens. To date only two EBNETs were preoperatively diagnosed based on the histological results of biopsies [77, 93]. Maybe, the routine uptake of brush cytology specimen during ERCP, percutaneous transhepatic cholangiography (PTC) or endoscopic ultrasound-guided fine needle aspiration and elaborate examination of the specimens will facilitate preoperative diagnosis.

Differential diagnosis should include adenocarcinoma (80 %), papillary adenocarcinoma (9.3 %), mucinous and mucin-producing adenocarcinoma (4.8 %), in situ carcinoma, squamous cell and adeno-squamous carcinoma, colloid carcinoma, oat-cell carcinoma, anaplastic carcinoma, pleomorphic giant cell tumor and sarcoma [72]. Additionally, benign epithelial tumors such as adenomas, cystadenomas and papillomas, granular cell tumors, rare lesions such asparaganglioma,

melanoma, lymphoma and botryoidrhabdomyosarcoma in children should be included in differential diagnosis [94]. When a primary bile duct neoplasm is suspected, differentiation between an unusual bile duct tumor, such EBNET and a cholangiocarcinoma is almost impossible prior to surgery and pathology report. Nevertheless, there are some features that differ between the two tumors and may help in preoperative suspicion of an EBNET; EBNET occurs more frequently in females and younger patients than adenocarcinoma, while aggressive local invasion by the primary tumor is rare in EBNETs, yet present in the majority of cholangiocarcinomas [62, 94]. Metastases are presented in 1/3 of EBNETs compared to 2/3 of all cholangiocarcinomas. Finally, total surgical resection is feasible in the vast majority of NETs, while curative resection of cholangiocarcinoma is feasible in only one-third of all cases [62].

EBNETs are slowly growing tumors and the only curative treatment up to date considered being the aggressive surgical resection. Biological characteristics of EBNETs demand radical surgical removal, in order to achieve complete tumor excision with negative histological margins [6, 62]. Preoperative decompression of biliary tree with stent placement still is controversial. Up to date in 24.5 % EBNET cases a stent was placed preoperatively to decompress the biliary ducts, but in one case described by Ross et al. [59] septic cholangitis developed after stent placement.

Primary tumors should be removed and local lymphadenectomy should be performed. If the tumor is deemed inoperable, debulking should be attempted [50]. Likewise, solitary liver metastases should be resected. The use of sophisticated devices in liver surgery, like radiofrequency devices, facilitated hepatectomies or allowed radiofrequency ablation in order to destroy the metastases [92]. When the distal bile duct is affected, surgery should consist of resection of the head of pancreas along with the whole of duodenum - with or without pyloric preservation – in order to achieve adequate radicality [17, 42, 59, 83]. If the tumor is localized in the middle or proximal bile duct, then an en bloc excision of the bile ducts - from the main hepatic ducts down to the upper margin of pancreas and adjoining lymph nodes– is necessary to preserve the patient's prospect of cure. The reconstruction should be made with Roux-en-Y hepaticojejunostomy or hepaticoduodenostomy [83]. Various types of hepatectomies should be attempted in tumors occurring in the hepatics bile ducts or hilar to achieve complete resection [46, 70, 72, 77]. Liver transplantation should be considered and fully justified, especially in young patients, when the tumor had a local-regional extension without distal metastases and traditional curative resection is not possible. Ki-67 index must be fully evaluated prior to attempt liver transplantation. Currently, this is the only curative option for these patients [72, 78].

There are numerous treatment options for patients with advanced EBNETs when surgery is not feasible. Medical treatment includes systemic chemotherapies, targeted therapies, somatostatin analogs, liver-directed therapies such as chemoembolization or thermoablation, and peptide receptor radionuclide therapy [110].

On pathology examination, the tumor's macroscopical features were nodular, infiltrating or polypoid. Most of them had argyrophilic cells without argentaffin cytoplasmic granules [72]. Histological features are similar to those of the intestinal NETs. They tend to grow in cords, nests or trabeculae and usually invade the ductal wall. Moreover, perineural and lymphovascular invasion is common [66]. From the immunohistochemical point of view, EBNET cells show positive staining for chromogranin, NSE, cytokeratins and synaptophysin. The biliary system is of foregut origin and, therefore, it is not surprising that immunoreactivity for serotonin, somatostatin and gastrin has been demonstrated for some of them [41, 52, 94]. Ki-67 index is also an important aspect of the baseline workup of EBNETs [94]. Well-differentiated EBNETs show a Ki-67 index of 2 % or less, while those of uncertain malignant potential show a Ki-67 index greater than 2 % [94]. In most of the cases the tumors are non-functional and clinically silent.

EBNETs have great variety in their aggressiveness. Those with typical neuroendocrine differentiation and minimal atypia (previously known as carcinoids) tend to be indolent in their behavior, whereas atypical neuroendocrine tumors may have more poorly differentiated or aggressive characteristics and worse prognosis. Atypical neuroendocrine tumors may have some histological features of adenocarcinomas [88]. Although malignant EBNETs are of an aggressive nature, they also tend to be less aggressive than the cholangiocarcinoma [62].

It is difficult to assess the prognosis of these tumors, since the cases are rare and long-term follow-up is often unavailable. In view of available data, these tumors seem to have better prognosis than bile ducts carcinomas after radical surgical treatment [77]. Although the size of the tumor, the presence of lympovascular invasion and the quantitative assessment of Ki-67 reactive cells help to determine prognosis, there are no absolute criteria for judging the malignant potential of EBNETs [7]. Noronha et al. [93] in her review suggests that the best predictor of malignant behaviour seems to be the size of the primary tumour, but based on our research this conclusion is unclear. 63.63 % of EBNETs (7/11) with size less than 1 cm had metastases, while the correspondence percentage for tumours ranging between 1 and 2 cm is 27.6 % (8/29) and that of tumours with size over 2 cm is 28.6 % (8/28). The WHO recently revised classification base mainly on the NET grade (mitotic index and ki-67 proliferation index). Based on our review, few cases of EBNETs display data concerning mitotic and Ki-67 index [6, 75]. We assume that the ranking of the EBNETs based on the grade will explain this observation, nevertheless these data are unavailable. Despite the small number of EBNETs appearing in

the literature, the long-term survival rate appears to be significantly better than in other types of biliary malignancies.

In conclusion, EBNETs are difficult to diagnose preoperatively because of their rarity, the absence of detectable serum markers and the usual lack of hormonal symptoms. Mitotic and Ki-67 index should be evaluated in all EBNETs to assess the grade of the tumors. Up to-date, the only curative treatment with good long-term results, for EBNETs, is aggressive surgical resection.

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