World Cancer Research Journal WCRJ 2019; 6: e1390

# MALIGNANT HILAR OBSTRUCTION DUE TO NEUROENDOCRINE TUMOR OF COMMON HEPATIC DUCT – A CASE REPORT AND SHORT REVIEW

K. SUNEED, P. ANSHUMAN, M. M. SHIBUMON, K. DINESH, J. SNEHA, C. SMITA, M. SHAKEEL

Department of Surgical Gastroenterology, Dr. RML Institute of Medical Sciences, Vibhuti Khand, Gomti Nagar, Lucknow, India.

**Abstract – *Objective:*** *Primary neuroendocrine tumors (NET) of the common hepatic duct are rare cause of malignant obstructive jaundice. Due to lack of specific features and inability to differentiate from hilar cholangiocarcinoma, they are diagnosed on postoperative histopathology. These tumors are potentially curable and usually require less aggressive surgical resection with good outcome.*

***Patient and Methods:*** *A 16-year-old boy presented with abdominal pain and intermittent jaundice. On cross-sectional imaging, a localized well-defined mass was detected in the common hepatic duct with associated locoregional lymphadenopathy.*

***Results:*** Patient underwent resection of the extra hepatic biliary tract with lymphadenectomy. Histopathology revealed moderately differentiated grade 2 NET, with positive immunohistochemical markers like Synaptophysin and Chromogranin. Targeted imaging with somatostatin receptor scintigraphy ruled out residual and metastatic disease. No adjuvant therapy administered, and kept on surveillance. He was disease-free at one-year follow-up.

***Conclusions:*** *Primary NET of the biliary tract is usually a postoperative diagnosis. If suspected preoperatively, evaluation with targeted imaging and limited, organ-preserving surgical excision yields good locoregional disease control along with satisfactory long-term outcomes.*

**KEYWORDS:** *Obstructive jaundice, Carcinoid, GEP NET, Bile duct.*

## INTRODUCTION

Nearly half of all extra hepatic bile duct malignancies are located in the hilar region. The commonest are cholangiocarcinoma (>80%)[1]. Uncommon causes include metastatic periportal lymphadenopathy and rare primary tumors of the biliary tract. Gastro-entero-pancreatic neuroendocrine tumor (GEP NET) of the extrahepatic biliary system is a rare primary tumor that has been reported in about 150 cases till date [1]. There is no consensus regarding their recommended management protocol, especially in the era of targeted imaging and therapeutic option. We present one such case of GEP NET who presented with obstructive jaundice, and managed surgically.

## CASE DESCRIPTION

A 16 year-old boy presented with upper abdominal pain of 18 months duration, and recurrent waxing and waning jaundice for 7 months. There was no history of cholangitis, anorexia or weight loss. On physical examination, he was icteric and poorly nourished with a body mass index of 17.4 kg/m$^2$. There were no remarkable abdominal findings. Biochemical investigations showed elevated total and direct bilirubin (5.89 and 3.50 mg/dL, respectively), raised alkaline phosphatase (529 U/L) and gamma glutamyl transferase (301 U/L). Tumor marker Carbohydrate Antigen (CA) 19.9 was 158.92 U/mL. Magnetic resonance cholangiopancreatography

*Corresponding Author:* Anshuman Pandey, MS; e-mail: suneed.kumar@gmail.com

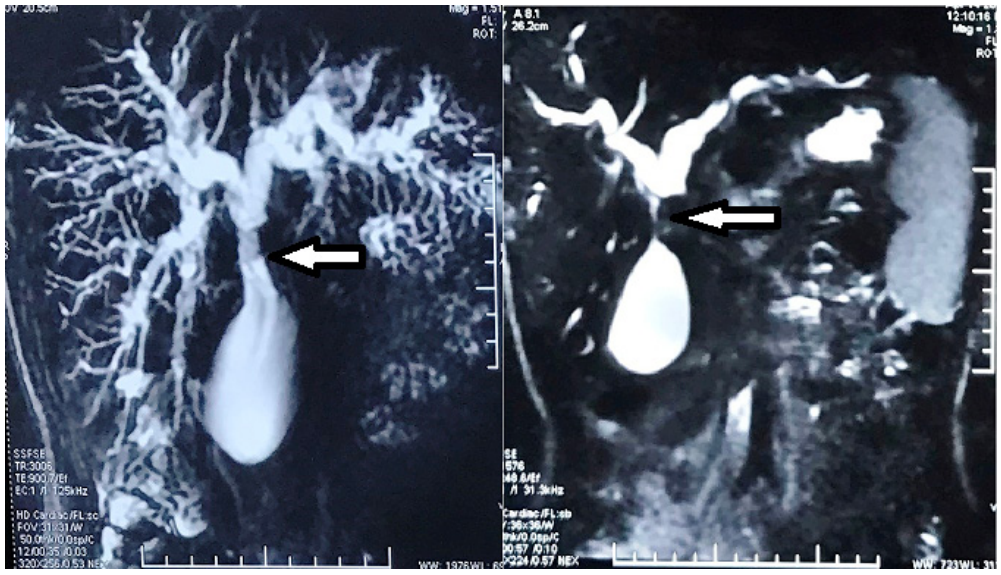

**Fig. 1.** MRCP images showing intraluminal filling defect at CHD-CBD-cystic duct junction. White arrows: Intramural mass.

(MRCP) revealed a focal intraluminal hypointense thickening of CHD causing a Bismuth-Corlette type I block (Figure 1). Triphasic computed tomography (CT) showed a heterogeneously enhancing mass at the CHD- common bile duct (CBD) junction. Multiple periportal and peripancreatic retroperitoneal lymph nodes were also presented (Figure 2). With a working diagnosis of hilar cholangiocarcinoma, he was planned for surgical resection. Intraoperatively, a well-defined hard mass, measuring 1 x 1 cm was noted in CHD just above the cystic duct insertion. The upper extent of tumor was grossly 2 cm below the biliary confluence (Figure 3a). The portal vein and hepatic arteries were not adherent to the tumor. The surgical plan was a radical excision of extrahepatic biliary tract, with frozen biopsies of proximal and distal margins. The need for associated hepatectomy would be decided based on the frozen reports. The procedure included dissection of the peripancreatic and periportal lymph nodes, while preserving the major vessels. The gall bladder along with entire extrahepatic biliary tract from confluence till supra-pancreatic portion was excised (Figure 3b). Since frozen biopsies from proximal and distal duct margin were negative for tumor infiltration, hepatectomy was deferred. Lymphadenectomy was continued along the common hepatic artery till right of the celiac trunk; with complete removal of lymph node stations 8a, 8p, 12a, 12b, 12p and 13. Biliary continuity was established with a Roux-en-Y Hepaticojejunostomy. A standard Blumgart type anastomosis with interrupted Vicryl 3-0 ® (Ethicon Inc, J&J Med-

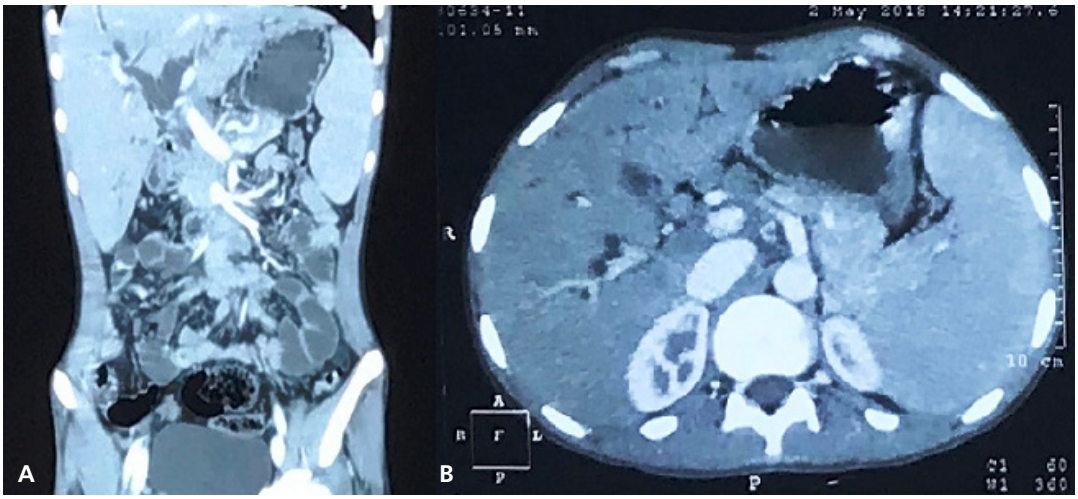


**Fig. 2.** Triple phase CT images showing biliary hilar obstruction by mass and multiple enlarged periportal lymph nodes. *A*, Coronal section; *B*, Axial section.

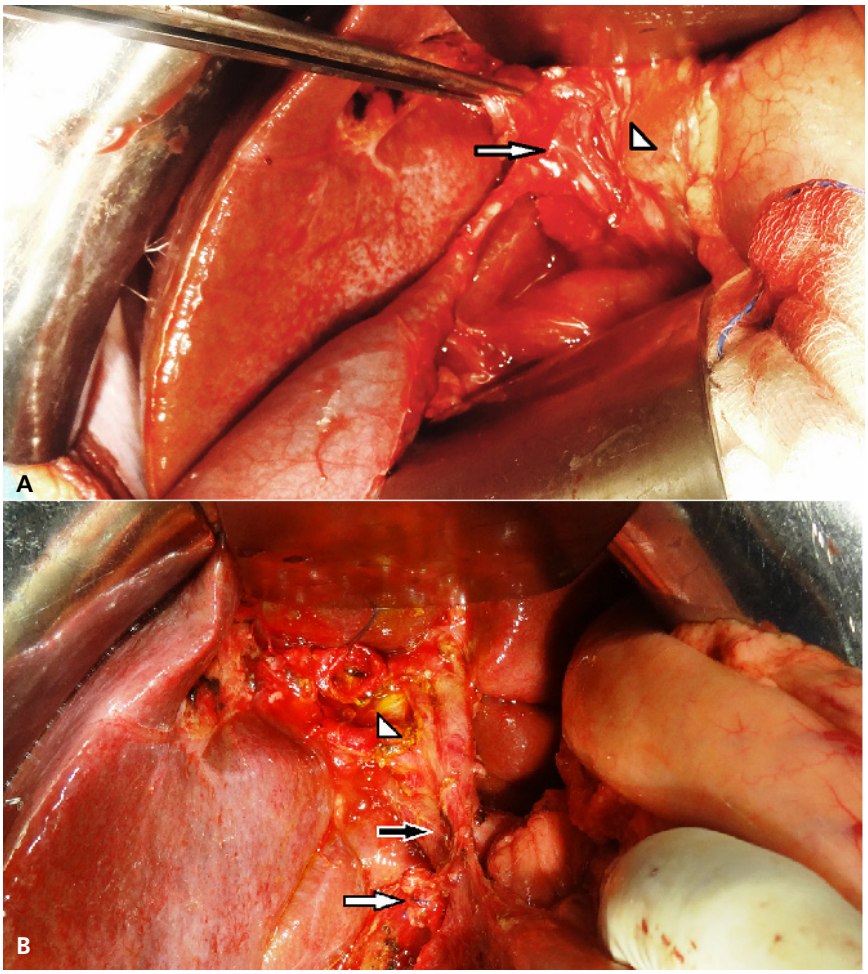


**Fig. 3.** *A*, Intra operative image showing mass at the CHD-CBD junction with dissected gall bladder. White arrow: Region of mass; White arrowhead: Periportal fibrofatty tissue containing lymph nodes. *B*, Intra operative image after resection of tumor with extra hepatic bile duct and periportal lymphadenectomy. White arrow: Distal stump of CBD; Black arrow: Portal vein; White arrowhead: Right hepatic artery.

ical Devices, Cincinnati, OH, USA) sutures were applied. A 28 Fr Romo-ADK® (Romsons, Agra, IN) abdominal tube drain system was inserted posterior to the anastomosis, and abdomen closed en-masse. Post-operative recovery was marked by chylous output from the drain. This was confirmed by raised drain-fluid triglyceride level. The drain was kept in situ, and patient managed conservatively with a combination of parenteral nutrition and medium-chain triglyceride diet. Patient was discharged from hospital in satisfactory condition with abdominal drain in-situ on 15$^{th}$ post-operative day. Daily drain output had reduced from nearly 1200 ml to about 200 ml at discharge. Histopathologic evaluation reported a moderately differentiated (G2) neuroendocrine tumor (Figure 4) confined to the CHD (pT1), mitotic count 0-1/10 hpf, Ki-67 proliferation index 5%, with positive lymphovascular and neurovascular invasion. Five out of sixty lymph nodes harvested were positive for metastasis (pN2). Immunohistochemistry (IHC) was positive for Synaptophysin and Chromogranin, negative for Cytokeratin (CK) 7 and CK 19 (Figure 5). A follow-up post-operative serum Chromogranin A assay and Tc-99m HYNIC-Noc Scintigraphy (Figure 6) showed no evidence of residual or metastatic disease. After discussion with multi-disciplinary team, adjuvant therapy was not administered, and patient was kept on close surveillance. A follow-up plan of 3 monthly serum Chromogranin A, 6 monthly cross-sectional imaging and annual scintigraphy was decided.

Two months post-surgery, the patient returned to us with sudden onset bilious output in the drain. On evaluation, drain erosion into the hepaticojejunostomy was confirmed; as depicted by the trans-tubal contrast study in Figure 7. This was managed conservatively by gradual drain withdrawal, which decreased the drain output. Drain was removed subsequently after the biliary drainage stopped. Patient was followed up till one-year post surgery, and was disease-free at last visit.

## DISCUSSION

Neuroendocrine tumors, better termed as GEP NET include a group of functional and non-functional tumors arising from multipotent entero-endocrine cells, situated all over the gastrointestinal tract. They are endodermal in origin. Although NETs account

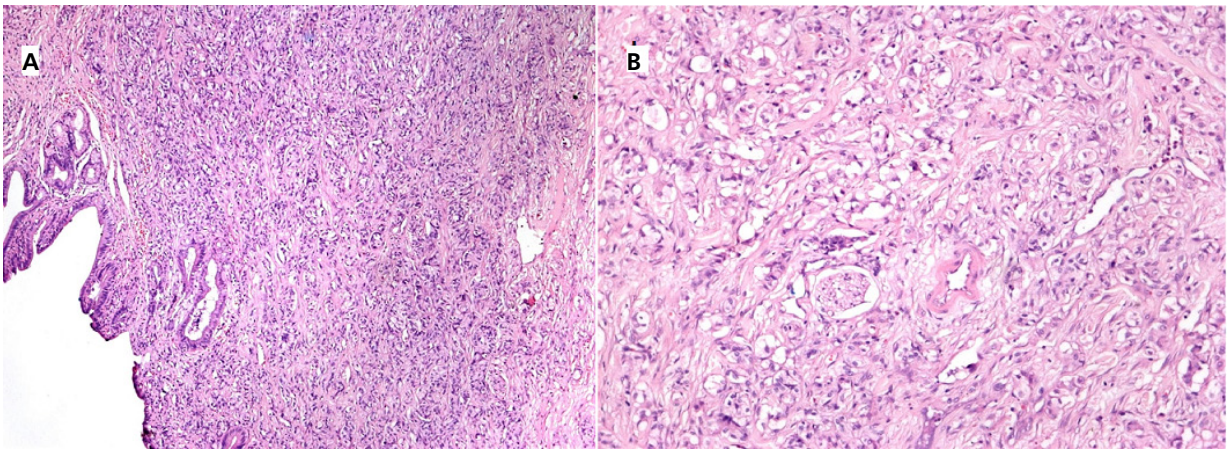


**Fig. 4.** Hematoxylin & Eosin (H & E) stained microscopy showing neuroendocrine morphology. *A*, 100X magnification; *B*, 400X magnification

for less than 2% of all GI tract malignancies, they are the second commonest malignancy affecting the organ system after colorectal cancer[2]. Most commonly located in the pancreas and small bowel, only 0.2-2% of GEP NETs involve the extrahepatic biliary tree[3].

Neuroendocrine tumors arise in the biliary tract as a sequela of chronic inflammation and intestinal metaplasia[5]. Nearly all cases are clinically silent, producing no detectable serum markers[6] Only five cases have been reported to have preoperative raised hormone levels producing symptoms[7-10]. Hence, the diagnosis of GEP NET of biliary tree is by postoperative histopathology. Due to the frequent masquerading as cholangiocarcinoma, preoperative tissue diagnosis is usually not performed in resectable disease. There have been reports of pre-operative diagnosis by endobiliary brush cytology[11,12].

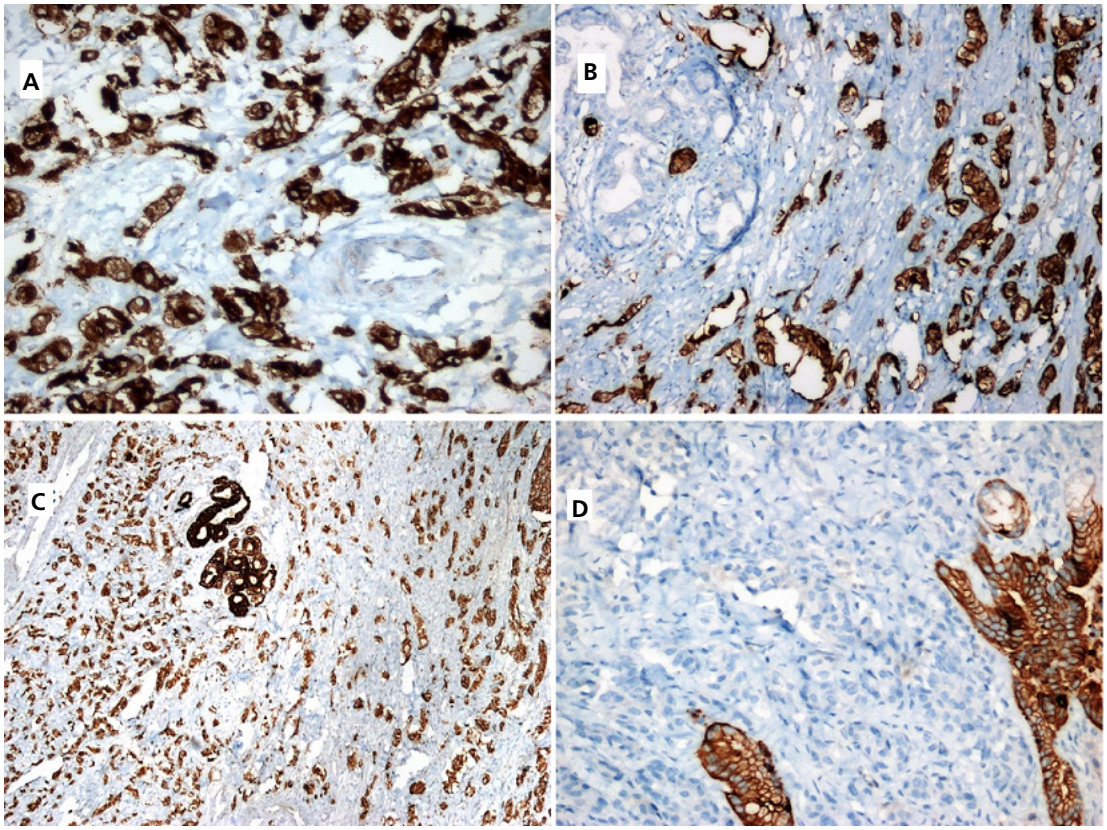


**Fig. 5.** Immunohistochemistry staining. *A*, Chromogranin Positive; *B*, Synaptophysin Positive; *C*, Pan CK stain Negative; *D*, CK 19 Negative

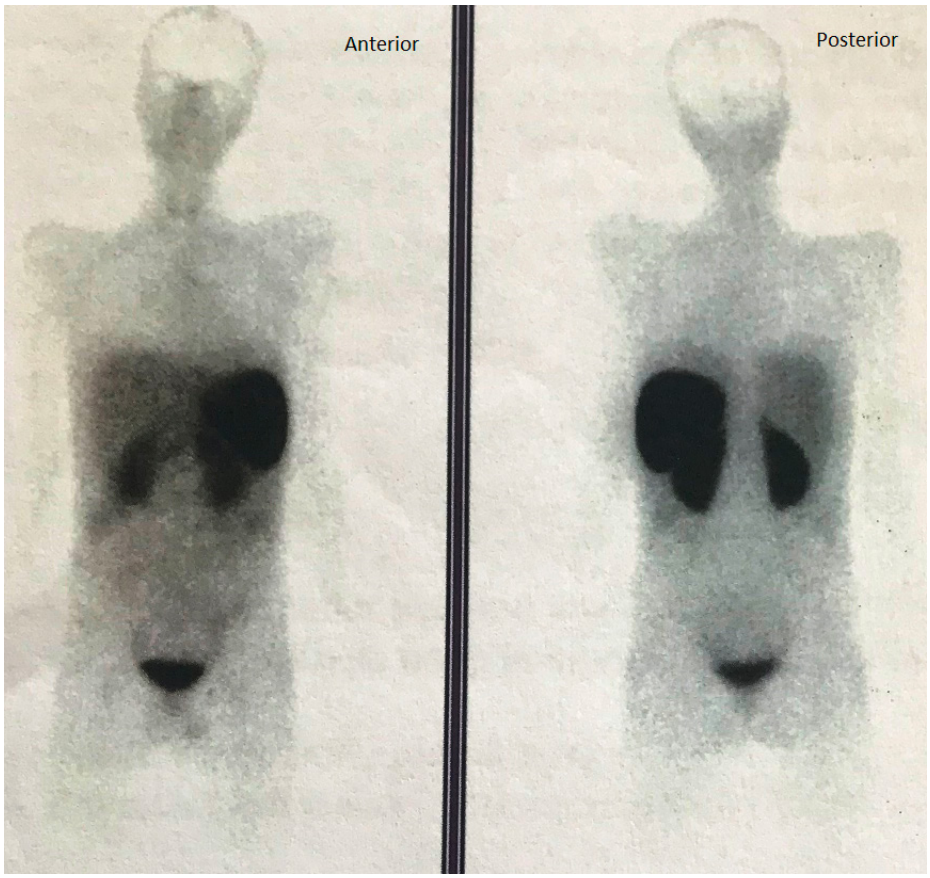


**Fig. 6.** Post-operative Tc-99 HYNIC TOC scintigraphy showing no residual or distant tumor uptake.

The pathology of GEP NET defines the clinical outcome and prognosis. The 2010 revised WHO classification of NETs is the most accurate and widely accepted, taking into consideration tumor size, number of mitosis per high-power-field, Ki-67 immunostaining (marker for cellular proliferation), vascular and perineural invasion[4]. Tumor grades are defined by mitotic number and Ki-67 index into G1, G2 and G3. Our patient had a moderately differentiated G2 tumor.

GEP NET of the extrahepatic biliary tract is slow growing indolent tumors with slight female preponderance. They are found commonly in the fourth to sixth decade of life [1]. Nearly 48% of cases arise

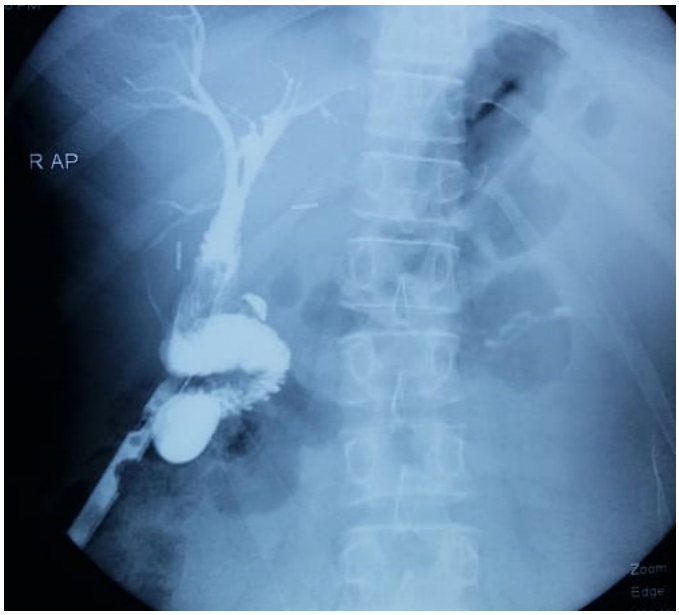


**Fig. 7.** Contrast study through abdominal drainage tube showing free flowing contrast proximally into biliary tree and distally into duodenum.

from the mid-CBD. Tumors arising in CHD and biliary bifurcation, like our case, account for 28.2% of all reported cases. According to the review by Michalopoulos et al[1], jaundice was the commonest presenting symptom, found in 60% cases, followed by abdominal pain (44%), pruritus (19%) and unexplained weight loss (15%). Tumor was incidentally detected in 10% cases. Disease was localized in nearly 65% cases, with locoregional spread in 4%, liver metastasis in 17% and lymph node involvement in about 20% cases.

In our case, sixty nodes were extracted as a part of standard lymphadenectomy. As a result, lymphorrhea occurred; requiring appropriate management. This required prolonged keeping of abdominal drain, leading to drain-related complications. The erosion of drainage tube into hollow viscous was fortunately managed without re-exploration.

Serum markers like Chromogranin A are elevated in NET, and indicative of tumor burden[3]. The postoperative values in our patients were normal, indicating complete clearance of tumor, and absence of systemic disease. Other markers like pancreastatin and pancreatic polypeptide have limited use in biliary tract NET. Tumor markers of biliary adenocarcinoma like CA 19.9 are non-specific for NET, and the raised value in our case was probably secondary to obstructive jaundice. Confirmation of systemic or disseminated disease is done by targeted imaging in the form of Somatostatin Receptor Scintigraphy (SRS) and positron emission tomography (PET). SRS or OctreoScan has reported sensitivity of 60 to 90% in pancreatic NET[13], which can be suitably extrapolated to biliary tract lesions.

Technicium-99-HYNIC-Toc scintigraphy provides a whole-body scan indicating dark spots where tracer uptake by somatostatin receptors is picked up by gamma camera. When combined with single photon emission CT, the diagnostic accuracy improves[13]. PET combined with CT is useful in locating tracers attached to Gallium-68 and Fluorine-18. 18F-fluorodeoxyglucose (FDG) is useful in locating poorly differentiated and high-grade NET. Somatostatin analogues, such as DOTA-Tyr(3)-octreotide (DOTATOC), DOTATyr(3)-octreotate (DOTATATE) and DOTA-1-Nal(3)-octreotide (DOTANOC), when linked to 68Ga offer better sensitivity, specificity and higher spatial resolution with PET in well differentiated GEP NET[14,15], and higher accuracy in identification of metastatic disease than SRS [16].

Curative treatment involves complete surgical resection of tumor with negative margins along with locoregional lymphadenectomy. R0 resection of NET results in better long-term outcomes compared to cholangiocarcinoma. Also, NET does not demonstrate the periductal spread that is seen commonly with cholangiocarcinoma. Hence, we can get away with a limited organ-preserving resection. In case of unresectable or inoperable disease, surgical debulking of primary tumor should be attempted, since it improves the outcomes in NETs. Liver metastasis does not preclude surgery, with established roles of resection and tumor ablation. In case of inoperable diseases, non-surgical therapy like somatostatin analogs, targeted radionuclide therapy, systemic chemotherapy and liver directed therapies have been described for NET from other primary sites, but not reported yet for biliary tract disease. Liver transplantation has also been reported for selected cases[17,18].

NET can be differentiated from cholangiocarcinoma by the following factors; involvement of younger females, lower metastasis rate (one third *vs*. two-thirds) and higher rate of R0 resectability[17]. NET is a diagnosis of histopathology, and has better prognosis than cholangiocarcinoma. According to the stage and grade of disease, some sort of therapy can be offered, to result in better quality of life and overall survival[19]. Hurdles in management of NET are the limited availability of specific imaging modalities, immunohistochemistry analysis, and targeted treatment options.

## CONCLUSIONS

Extrahepatic biliary tract NETs are a rare cause of obstructive jaundice. With limited surgical resection, they offer better overall prognosis than cholangiocarcinoma. The need to evaluate such cases with targeted imaging to rule out disseminated disease is reiterated.

**Statement of interest:**
None of the authors have any conflicts of interest or any financial support to disclose.

**Informed Consent:**
The participant in this study signed the informed consent.

## REFERENCES

1. Michalopoulos N, Papavramidis TS, Karayannopoulou G, Pliakos I, Papavramidis ST, Kanellos I. Neuroendocrine Tumors of Extrahepatic Biliary Tract. Pathol Oncol Res 2014; 20: 765-775.
2. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008; 26: 3063-3072.
3. Modlin IM, Sandor A. An analysis of 8305 cases of carcinoids tumors. Cancer 1997; 79: 813-819.

4. Rindi G, Arnold R, Bosman FT, Capella C, Klimstra DS, Kloppel G, Komminoth P, Solcia E. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND (eds) WHO Classification of Tumors of the Digestive System, 4th edn. (2010) International Agency for Research on Cancer, Lyon, pp. 13-14.
5. Todoroki T, Sano T, Yamada S, Hirahara N, Toda N, Tsukada K, Motojima R, Motojima T. Clear cell carcinoid tumor of the distal common bile duct. World J Surg Oncol 2007; 5: 6.
6. Lombardi A, Batignani G, Nesi G. Primary carcinoid tumour of the common bile duct. HPB 2000; 2: 95-100.
7. Little JM, Gibson AA, Kay AW. Primary common bile-duct carcinoid. Br J Surg 1968; 55: 147-149.
8. Nesi G, Lombarti A, Batignani G, Ficari F, Rubio CA, Tonelli F. Well-differentiated endocrine tumor of the distal common bile duct: a case study and literature review. Virchows Arch 2006; 449: 104-111.
9. Martignoni ME, Friess H LubkeD, Uhl W, Maurer C, Müller M, Richard H, Reubi JC, Büchler MW. Study of a primary gastrinoma in the common hepatic duct – a case report. Digestion 1999; 60: 187-190.
10. Price TN, Thompson GB, Lewis JT, Lioyd RV, Young WF. Zollinger-Ellison syndrome due to primary gastrinoma of the extrahepatic biliary tree: three case reports and review of the literature. Endocr Pract 2009; 15: 737-739.
11. Hubert C, Sempoux C, Berquin A, Deprez F, Jamar F, Giqot JF. Bile duct carcinoids tumors: an uncommon disease but with a good prognosis? Hepatogastroenterol 2005; 52: 1042-1047.
12. Malecki EA, Acosta R, Twaddell W, Heller T, Manning MA, Darwin P. Endoscopic diagnosis of a biliary neuroendocrine tumor. Gastrointest Endoscopy 2009; 70: 1275-1276.
13. Lu SJ, Gnanasegaran G, Buscombe J, Navalkissoor S. Single photon emission computed tomography/computed tomography in the evaluation of neuroendocrine tumours: a review of the literature. Nucl Med Commun 2013; 34: 98-107.
14. Sundin A. Radiological and nuclear medicine imaging of gastroenteropancreatic neuroendocrine tumours. Best Pract Res Clin Gastroenterol 2012; 26: 803-818.
15. Naswa N, Sharma P, Kumar A, Nazar AH, Kumar R, Chumber S, Bal C. Gallium-68-DOTA-NOC PET/CT of patients with gastroenteropancreatic neuroendocrine tumors: a prospective single center study. Am J Roentgenol 2011; 197: 1221-1228.
16. Maxwell JE, Howe JR. Imaging in neuroendocrine tumors: an update for the clinician. Int J Endocr Oncol 2015; 2: 159-168.
17. El Rass ZS,Mohsine RM, Berger F, Thierry P, Partensky CC. Endocrine tumors of the extrahepatic bile ducts. Pathological and clinical aspects, surgical management and outcome. Hepatogastroenterol 2004; 51: 1295-1300.
18. Tzimas GN, Vali K, Deschenes M, Marcus VA, Barkun JS, Tchervenkov JI, Metrakos PP. Liver transplantation for metastases from a bile duct carcinoid. HPB 2006; 8: 67-68.
19. Jiménez-Fonseca P, Carmona-Bayonas A, Martín-Pérez E, Crespo G, Serrano R, Llanos M, Villabona C, Garcia-Carbonero R, Aller J. Capdevila J. Grande E. Health-related quality of life in well-differentiated metastatic gastroenteropancreatic neuroendocrine tumors. Cancer Metastasis Rev 2015; 34: 381-400.