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CASE REPORT

Intrahepatic Cholangiocarcinoma: case report and review of literature

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Abstract

Background: Intrahepatic cholangiocarcinoma (ICC) is a rare primary hepatic cancer that poses a challenge to early diagnosis and curative treatment. The prognosis is poor if untreated. There is a paucity of literature on intrahepatic cholangiocarcinoma in Nigeria. Here, we report a case of an early ICC who had a segmental resection of the liver at the University of Benin Teaching Hospital with a good outcome.

Aim and objective: To highlight the essential steps in the diagnosis and treatment of intrahepatic cholangiocarcinoma and demonstrate that liver resections can be performed safely in our setting.

Case report: We present a 45-year-old woman with a peripheral intrahepatic cholangiocarcinoma. She had an MRI which revealed a unifocal lesion in segments V and VI. Reports of assay of Alpha-fetoprotein (AFP), Carcinoembryonic antigen (CEA), and Ca 19-9 showed normal values. She had resection of segments V and VI with lymphadenectomy of the hilar lymph nodes. The margins of resection were free of mitotic lesions and the lymph nodes revealed reactive hyperplasia on histologic analysis. She had a course of adjuvant Capecitabine therapy. After 18 months of follow-up, there were no clinical or radiologic (MRI) signs of tumour recurrence.

Conclusion: The case presented is to the best of our knowledge the first reported case of intrahepatic cholangiocarcinoma that was managed with good outcome in Nigeria. It highlighted an alignment with the known standard of care for intrahepatic cholangiocarcinoma and, the first major liver resection in the University of Benin Teaching Hospital. Early diagnosis and adequate surgical resection may provide the only hope of prolonging survival and possibly achieving a cure.

Keywords: Intrahepatic cholangiocarcinoma; Liver cancer; Liver resection.

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Introduction

Primary liver cancer is the 6th most common cancer and the 3rd leading cause of cancer death.[1] Cholangiocarcinoma is second only to hepatocellular carcinoma among primary liver cell cancers. It constitutes 15% of all liver cancers and 3% of all gastrointestinal cancers.[1-5] Cholangiocarcinoma arises from the biliary epithelium and it is anatomically classified into intrahepatic cholangiocarcinoma, perihilar/hilar cholangiocarcinoma and distal cholangiocarcinoma[6,7]. The perihilar and distal cholangiocarcinoma constitute the extrahepatic cholangiocarcinoma (Figure 1). Its further histomorphologic and molecular classifications bear prognostic and possibly therapeutic implications in the future, as surgery remains the only chance of cure for now [6, 8, 9].

Intrahepatic cholangiocarcinoma (ICC) constitutes about 10% of cholangiocarcinoma with a median survival of about 13 to 36 months.[3,10] Identifiable risk factors for intrahepatic cholangiocarcinoma are hepatolithiasis, infestations with helminths, and sclerosing cholangitis[1]. Approximately 50% of cases have no known risk factors in resource-rich settings.[9]

There are no specific clinical features of ICC and no known screening protocol. These pose challenges to early diagnosis. Those apparently diagnosed early usually present with nonspecific symptoms or are found while investigating for other disease conditions and constitute only a sixth to a third of patients amenable to curative surgical resection.[3, 9, 11] The diagnosis is essentially based on radiologic investigations such as abdominal ultrasonography, computed tomography, Magnetic resonance imaging; and image-guided percutaneous biopsy of the liver lesion for histologic analysis. Surgical resection offers the only chance of curative treatment [2]. Other modalities of treatment are mainly palliative.[3] Given that most liver cancers are secondary, it is worthwhile to explore the primary sites of the metastatic lesions during the diagnostic work-up of patients with liver tumours. Radiologic and endoscopic investigations are key in the exploration of well-established sites such as the breast, lung, and colorectum that metastasize to the liver.[1, 12.]

There is a paucity of literature on intrahepatic cholangiocarcinoma in Nigeria.[13]

Here, we report a case of intrahepatic cholangiocarcinoma that presented early to the general surgical services of the University of Benin Teaching Hospital, South Nigeria and had segmental resection of the liver with a good outcome. This would add to the very few literatures on ICC in Nigeria.[13]

This case study is aimed at highlighting the essential steps in the diagnosis and treatment of ICC, and to show that curative hepatic resections are feasible and safe in our setting.

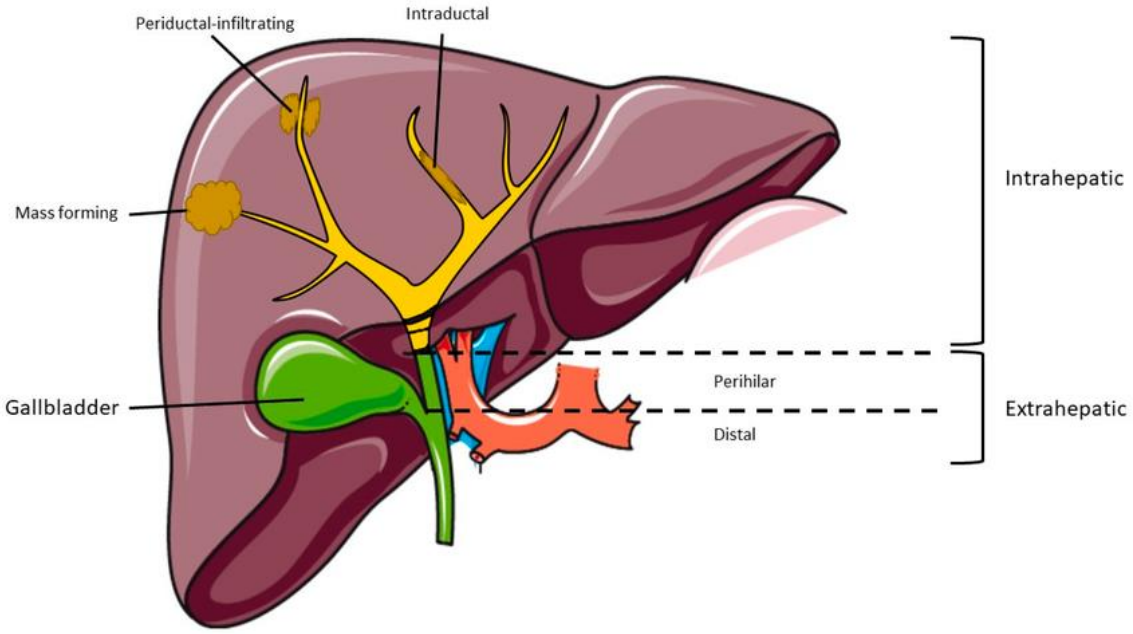

Figure 1: Classification of cholangiocarcinoma by anatomic location from Management of Intrahepatic Cholangiocarcinoma by Sudha KA et al[17]

Case presentation

A 45-year-old woman presented with recurrent right upper quadrant abdominal pain of one-month duration. The pain was dull, intermittent, and radiated to the epigastrium and right lumbar region. There was no anorexia, nausea, vomiting, change in bowel habit, passage of blood/mucus in stool, abdominal distension, yellowness of the eyes, fever, or weight loss. No chronic medical illnesses. No known family history of similar lesions or malignancies. Physical examination revealed an ill-looking woman, not pale, anicteric with a right hypochondriac intrabdominal mass that is mobile on the horizontal plane, hard, and 6cm below the costal margin with a bosselated surface and margin. Complete blood count values were

normal. Alkaline phosphatase was noticed to be markedly elevated, but other liver enzymes were essentially normal. Tumour markers (CEA, Alpha-fetoprotein, and CA19-9) were normal. Colonoscopy findings were also normal. Abdominal computed tomography scan showed heterogeneously enhancing right lobe hypodense solid mass involving segments V and V1. Abdominal magnetic resonance imaging showed a right hepatic mass (Figure 2). Ultrasound-guided biopsy for histologic analysis revealed intrahepatic cholangiocarcinoma.

Intraoperatively she had a right subcostal incision. The findings at laparotomy were a huge tumour with a nodular surface involving the superior and inferior surfaces of the right lobe (segments V and VI) and enlarged multiple lymph nodes at the porta hepatis. The left lobe and gallbladder were normal. The patient had resection segmentectomy using the clamp crushing technique and electrocautery, and excision of the enlarged lymph nodes (Fig 3). Bleeding from the liver was controlled by applying the pringle maneuver with a bulldog clamp, electrocautery, and the use of 3/0 Polyglactin 910 sutures to ligate the intrahepatic vessels. The intrahepatic biliary radicles were carefully ligated with 3/0 Polyglactin sutures. A closed tube drain was left in Morrison's pouch and the greater omentum was brought near the exposed liver surface. The right subcostal incision was closed in layers, and Polyethylene 2/0 sutures were used for mattress skin closure. There was no need for blood transfusion.

She had an uneventful recovery from the surgery and was discharged on postoperative day 8. Histopathology confirmed the diagnosis of intrahepatic cholangiocarcinoma, and the excised lymph nodes were free of metastatic deposits (Figures 4 and 5). She had 6 cycles of adjuvant cytotoxic chemotherapy with capecitabine. She has had 18 months of follow-up, and there are no clinical or radiologic features of tumour recurrence.

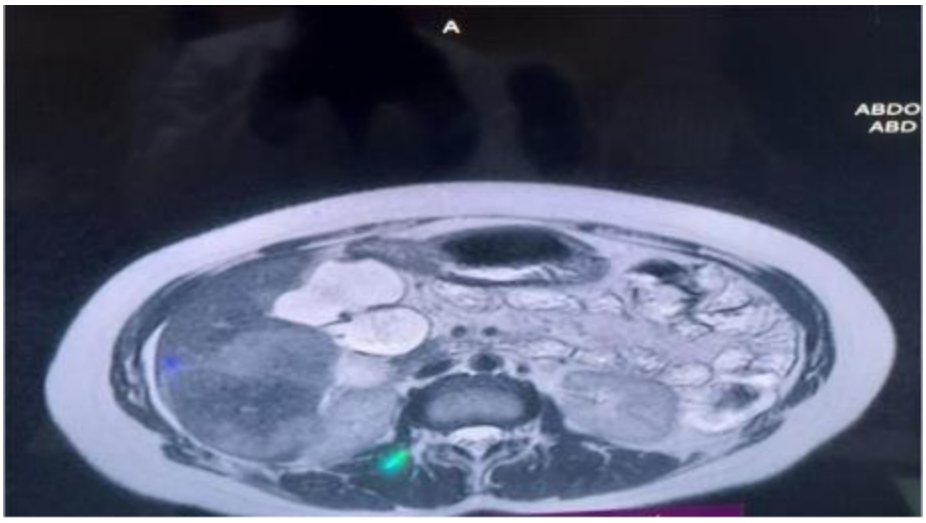

Figure 2: MRI showing the tumour in the liver.

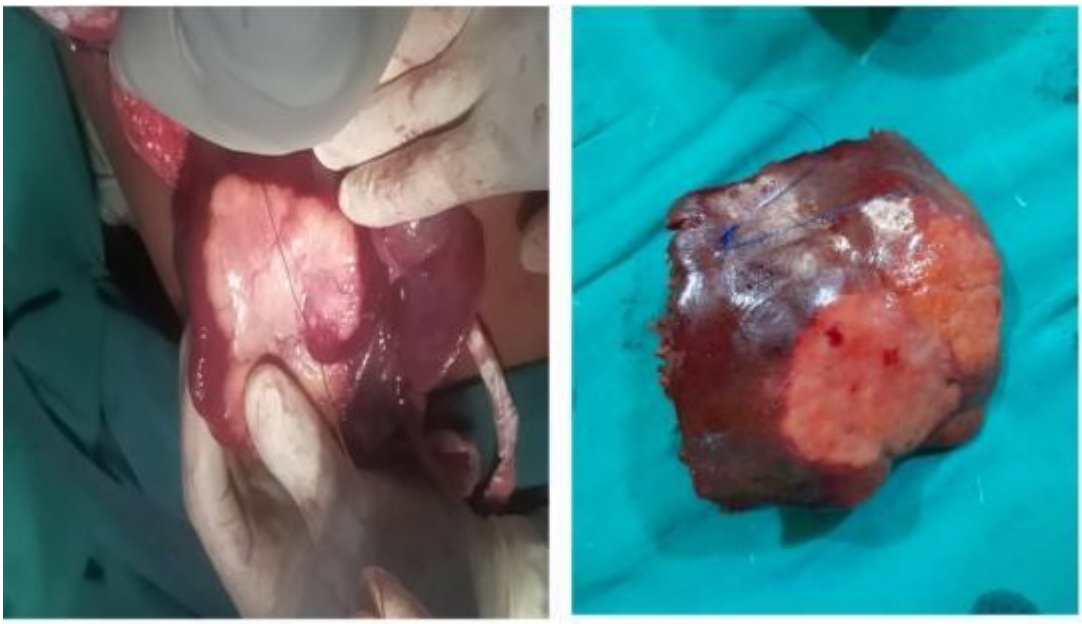

Figure 3: Resected portion of the liver containing intrahepatic cholangiocarcinoma in segments V and VI.

Discussion

Cholangiocarcinoma is a rare and aggressive tumour that arises from the epithelium of the biliary tract.[4] It is the second most common primary hepatic neoplasm. Most of the time, its classification is based on its location such as intrahepatic and extrahepatic cholangiocarcinoma.[4,5,9] (Figure 1). This

classification greatly impacts its management.[9,14] The new histomorphologic and molecular classification of intrahepatic cholangiocarcinoma bears prognostic, and possibly therapeutic implications in the future.[6,8,9.]

Intrahepatic cholangiocarcinoma is more common in males with racial diversity. The peak incidence of ICC occurs between the ages of 55 and 75 years. It is extremely rare before the age of 45 (less than 10% of patients).[7] This is contrary to the case reported here where the index patient is a female and aged 45 years. This could be due to underreporting of cases, late presentation, and the death of patients even before the diagnosis is made.

The incidence of intrahepatic cholangiocarcinoma (ICC) in the Western world is approximately 1-2 per 100,000. Attributable to 3% of all cases of gastrointestinal cancer, ICC is the second most prevalent cancer found in the liver.[4, 7] ICC accounts for 10% of all cholangiocarcinoma[15]. It originates in the liver parenchyma's peripheral bile ducts, close to the secondary biliary radicals. It needs to be differentiated from distal cholangiocarcinoma, which arises close to the pancreatic head, and perihilar cholangiocarcinoma, which arises close to the biliary confluence.[16, 17] At the time of diagnosis, only 15% of ICC patients present with resectable disease.[17] With a median survival predicted to be between 27 and 36 months, complete surgical resection is still the only option for cure [17] When they are first diagnosed, more than 75% of the patients are older than 65 years. ICC is slightly more common in men, and in East Asia; in the People's Republic of China, an incidence of 10 per 100,000 persons has been reported, while in Thailand, the incidence is 71 per 100,000; which is higher than that of hepatocellular carcinoma (HCC).[18]

Most ICC arise denovo without identifiable risk factors as seen in the index case. However, risk factors such as primary sclerosing cholangitis, primary biliary cirrhosis, congenital malformations of the bile duct (i.e., choledochal cysts), hepatolithiasis, hepatitis B and C virus, alcoholic liver cirrhosis, smoking, hepatic parasite infections, in particular (Opisthorchis viverrini and Clonorchis sinensis) are all implicated in the evolution and the pathogenesis of the disease.[2,17-20] Genetic and environmental factors have

been responsible for the vast difference in incidence between the East and West. [19]

The clinical presentation of IHC is similar to that of HCC[15, 20]. It is usually asymptomatic in the early stages. Most patients present with nonspecific symptoms, such as abdominal pain in the right upper quadrant and weight loss. Jaundice occurs less commonly because these tumours tend to arise in the periphery of the liver.[20] It could be an incidental finding on imaging for another abdominal pathology. Our patient presented with right upper abdominal pain and had no jaundice or weight loss.

The Alpha-fetoprotein level (AFP) is usually normal, unlike HCC, as seen in the index case. Carcinoembryonic antigen (CEA) and CA19-9 levels could be elevated in some cases of metastatic adenocarcinoma of the liver.[15, 21.] However, these were normal in the index patient. Abdominal ultrasound is the first imaging modality of choice in assessing patients with biliary tract disease, as seen in the index patient. This is due to its attendant benefits of availability, nonionizing, and sensitivity in detecting hepatobiliary lesions. It often detects a liver mass with or without dilatation of the biliary tract[15,21]. The number of lesions and, vascular involvement are determined using a dual-phase multi-detector Computer tomography scan (CT). On unenhanced CT scans, an ICC typically appears as a hypodense mass with irregular edges. In the arterial contrast-enhancement phase, peripheral rim enhancement occurs, and in the portal-venous and delayed contrast-enhancement phases, progressive contrast uptake occurs.[15, 22] It can be challenging to differentiate small ICCs from HCC.

Magnetic resonance cholangiopancreatography (MRCP) has good accuracy for diagnosis and assessment of the extent of the tumor and plan for surgical resection. MRCP has a diagnostic accuracy of up to 93% and is recommended for visualization of the tumour extension in the ductal system and vascular structures.[21, 22] Preoperative positron emission tomography (PET) scan may be considered to help rule out occult metastatic disease, as PET changes surgical decision making in up to 30% of patients.[20-23.] Artificial intelligence has been proposed to mitigate the challenges of early diagnosis of intrahepatic cholangiocarcinoma[2].

The case reported had an abdominal Ultrasound scan as the initial investigation.

She had an abdominopelvic CT scan and Colonoscopy to rule out lesions in sites that commonly metastasize to the liver[1]. An abdominal ultrasound-guided percutaneous biopsy of the liver tumour and subsequent histologic analysis confirmed intrahepatic cholangiocarcinoma. The Magnetic resonance imaging was done for proper delineation of the liver segments that habour the liver tumour and to plan the intervention that would be appropriate to achieve complete resection. (Figure 2). The preferred modality of treatment is complete resection.[15] The role of chemotherapy and radiotherapy have not been proven to be effective in the management of primary disease.[4, 15, 20]. Our patient had a laparotomy and the tumour involved segments V and VI of the liver. No other abnormalities were found. A resection with a tumour-free macroscopic margin was done with clamp crushing technique and electrocautery (Figure 3). The enlarged perilesional lymph nodes were also excised. Histopathology examination confirmed intrahepatic cholangiocarcinoma with tumour-free margins and the lymph nodes free of tumour deposits (Figures 4 and 5). Capecitabine chemotherapy was used in the index patient because some studies found it to be effective as an adjuvant in the treatment of biliary cancers.[24,25] Given the tumour-free resection margins and lymph nodes, close follow-up is necessary, as the 5-year survival rate remains low despite curative-intent surgery.[26]

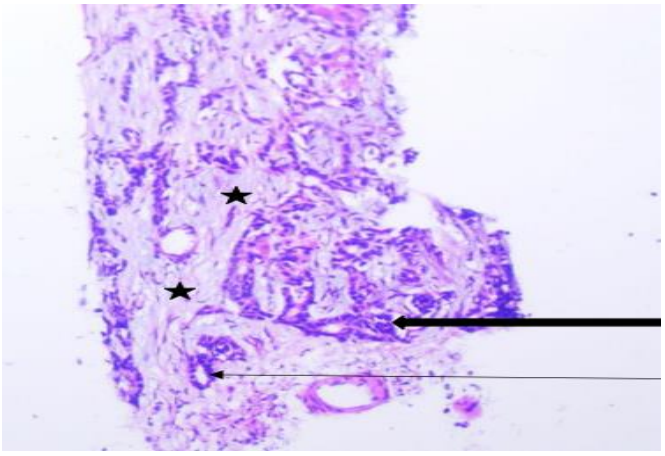

Figure 4: A micrograph of a strand of liver tissue that has been completely effaced by a malignant neoplastic lesion comprising small tubular glands (thin arrow) and cribriform glandular structures (thick arrow) lined by atypical cuboidal cells within the fibrous stroma (H&E x100 magnification).

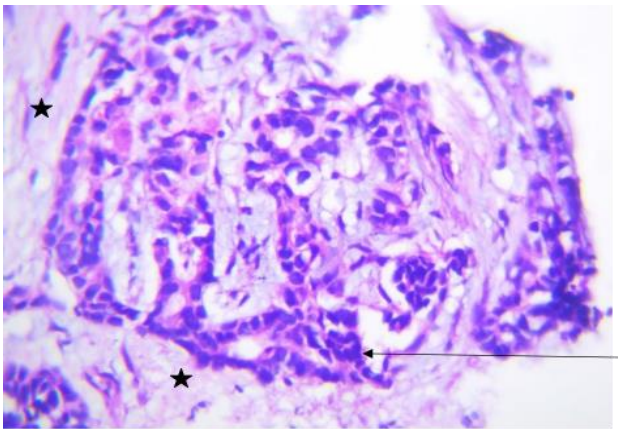

Figure 5: A micrograph of liver tissue completely effaced by a malignant neoplastic lesion composed of cribriform glands (arrow) separated by fibrous stroma (stars). The glands are lined by atypical cuboidal epithelial cells exhibiting nuclear hyperchromasia and pleomorphism. The nuclear pleomorphism in lining epithelium within a single gland is a common diagnostic feature (H&E x 400 magnification)

Conclusion

This is a case of intrahepatic cholangiocarcinoma that was managed successfully. It is probably the first reported case of intrahepatic cholangiocarcinoma that was managed with good outcome in Nigeria. The resection of this tumour is the first major liver resection at the University of Benin Teaching Hospital. We advocate that adult patients presenting with upper abdominal pain as their sole complaint in our region should have an abdominal ultrasound scan, along with other necessary investigations deemed fit by the attending physician. Early diagnosis and adequate surgical resection may provide the only hope of prolonged survival and the possibility of achieving a cure for intrahepatic cholangiocarcinoma.

References

1. Ananthakrishnan A, Gogineni V, Saeian K. Epidemiology of primary and secondary liver cancers. *Seminars in Interventional Radiology.* 2006; 23(1):47-63.
2. Granata V, Fusco R, De Muzio F, Cutolo C, Grassi F, Brunese MC et al. Risk Assessment and Cholangiocarcinoma: Diagnostic Management and Artificial Intelligence. *Biology.* 2023; 12(2):213.
3. Buettner S, van Vugt JL, IJzermans JN, Groot Koerkamp B. Intrahepatic cholangiocarcinoma: current perspectives.

Onco Targets and Therapy. 2017; 10:1131-1142.

4. Asombang AW, Chishinga N, Mohamed FM, Nkhoma A, Chipaila J, Nsokolo B, et al. Systematic review of cholangiocarcinoma in Africa: epidemiology, management, and clinical outcomes. *BMC Gastroenterology*. 2023; 23(1):1-10.
5. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology.* 2001; 33(6):1353-1357.
6. Kendall T, Verheij J, Gaudio E, Evert M, Guido M, Goeppert B et al. Anatomical, histomorphological, and molecular classification of cholangiocarcinoma. *Liver International*. 2019; 39(1):7-18.
7. Shaib YH, El-Serag HB, Davila JA, Morgan R, McGlynn K. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. *Gastroenterology*. 2005; 128(3):620–626.
8. Zhang H, Yang T, Wu M, Shen F. Intrahepatic cholangiocarcinoma: epidemiology, risk factors, diagnosis and surgical management. *Cancer Letters*. 2016;379(2):198-205.
9. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. *Liver International*. 2019; 39(1):19–31.
10. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. *Nature Reviews Gastroenterology & Hepatology*. 2011; 8(9):512-22.
11. Bergquist A. Von Seth E. Epidemiology of cholangiocarcinoma. *Best Practice & Research Clinical Gastroenterology*. 2015; 29(2):221-232.
12. Wang ZG, He ZY, Chen YY, Gao H, Du XL. Incidence and survival outcomes of secondary liver cancer: a Surveillance Epidemiology and End Results database analysis. *Translational Cancer Research.* 2021; 10(3):1273-1283.
13. Ugiagbe EE, Udoh MO. The histopathological pattern of liver biopsies at the University of Benin Teaching Hospital. *Nigerian Journal of Clinical Practice.* 2013;16(4):526-529.
14. Malhi H, Gores GJ. Cholangiocarcinoma: modern advances in understanding a deadly old disease. *Journal of Hepatology*. 2006; 45(6):856–867.
15. Townsend MC, Beauchamp DR, Mark Evers, Kenneth L. Liver. The biological basis

of modern surgical practice. Elsevier;20th edition. 2017. P. 1464

16. Kirstein MM, Vogel A. Epidemiology and Risk Factors of Cholangiocarcinoma. *Visceral Medicine*. 2016; 32(6):395–400.
17. Bragazzi MC, Cardinale V, Carpino G, Venere R, Semeraro R, Gentile R et al. Cholangiocarcinoma: Epidemiology and risk factors. *Translational Gastrointestinal Cancer.* 2012; 1(1):21-32.
18. Kodali S, Shetty A, Shekhar S. Victor DW, Ghobrial RM. Ghobrial. Management of Intrahepatic Cholangiocarcinoma. *Journal of Clinical Medicine*. 2021; 10(11):2368-2369.
19. Bartella I, Dufour JF. Clinical Diagnosis and Staging of Intrahepatic Cholangiocarcinoma. *Journal of Gastrointestinal & Liver Disease*. 2015;24(4):481-489.
20. Weber A, Schmid RM, Prinz C. Diagnostic approaches for cholangiocarcinoma. *World Journal of Gastroenterology.* 2008;14(26):4131-4136
21. Van beers BE. Diagnosis of cholangiocarcinoma. *Journal of the International Hepato-Pancreato-Biliary Association*. 2008; 10(2):87-93
22. Archampong EA, Naader SB, Ugwu BM. Ultrasound scanning, Computerized Tomography, Magnetic Resonance Imaging and radioisotope Scanning. Principles and Practice of Surgery. Ghana Publishing Corporation. 5th edition. 2015. Pp 1428-1465.
23. Fábrega-Foster K, Ghasabeh MA, Pawlik TM, Kamel IR. Multimodality imaging of intrahepatic cholangiocarcinoma. *Hepatobiliary surgery and Nutrition*. 2017;6(2):67-78.
24. Qu WF, Liu WR, Shi YH. Adjuvant chemotherapy for intrahepatic cholangiocarcinoma: far from a clinical consensus. *Hepatobiliary Surgery and Nutrition.*2021; 10(6):887-889.
25. Ma KW, Cheung TT, Leung B, She BWH, Chok KSH, Chan ACY et al. Adjuvant chemotherapy improves oncological outcomes of resectable intrahepatic cholangiocarcinoma: A meta-analysis. *Medicine*. 2019; 98(5):1-10.
26. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and Prognosis for Patients with Intrahepatic Cholangiocarcinoma: Systematic Review and Meta-analysis. *JAMA Surgery*. 2014;149(6):565-574.