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Review Article

Comprehensive review of Cholangiocarcinoma

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Abstract

Cholangiocarcinoma (CCA), a malignant neoplasm originating from the biliary epithelium, represents the second most common primary hepatic tumor, accounting for 10–15% of hepatobiliary malignancies. This scientific session aimed to provide a comprehensive overview of CCA, encompassing its epidemiology, risk factors, pathogenesis, clinical presentation, diagnostic approaches, and management strategies. CCA is broadly classified into intrahepatic, perihilar, and distal types, each with unique clinical implications. Risk factors include primary sclerosing cholangitis, liver fluke infection, bile duct cysts, and chronic liver diseases, which contribute to chronic inflammation and malignant transformation of cholangiocytes.

Diagnosis of CCA remains challenging due to its often late presentation and nonspecific symptoms. Advancements in imaging techniques, including MRI and MRCP, combined with tumor markers such as CA 19-9, have improved diagnostic accuracy. However, histopathological confirmation remains essential. Treatment strategies depend on the tumor's location and stage. Surgical resection offers the only potential cure but is feasible in a limited number of patients. In unresectable cases, chemotherapy, radiotherapy, and emerging targeted therapies are employed to prolong survival and improve quality of life. Liver transplantation is considered in select early-stage perihilar CCA cases under stringent criteria.

The session emphasized the importance of early detection, multidisciplinary management, and continued research into novel therapeutic approaches. Awareness and education on the risk factors and symptoms of CCA are crucial in improving patient outcomes. Overall, this session served as a valuable platform for enhancing clinical understanding and fostering collaborative efforts in the fight against cholangiocarcinoma.

Keywords

Cholangiocarcinoma, intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, management of cholangiocarcinoma, risk factor for cholangiocarcinoma

Introduction

Cholangiocarcinoma (CAA) is the second most common primary neoplasm of the hepato-biliary apparatus, accounting for 3% of all gastrointestinal malignancies and 10–15% of hepatobiliary malignancies. CCA arises from the malignant transformation of cholangiocytes, the epithelial cells lining the intra and extrahepatic bile ducts [1]. It is seldom diagnosed in patients younger than 40, with the peak incidence between the fifth and seventh decade of life [2]. It affects men more frequently than women, with ratios of 1.2–1.5 per 100,000 and one per 100,000 people, but the incidence increases with age in both sexes [3].

The development of cholangiocarcinoma is a multi-step process dependent on an interaction between environmental factors and host genetic factors. The molecular mutations of CCA occur because of Prolonged exposure of cholangiocytes to inflammatory mediators (e.g., tumour necrosis factor-α, interleukin-6, and cyclo-oxygenase-2), and subsequent chronic inflammatory reaction leads to mutations in oncologic genes. Inflammation-induced impaired bile flow leads

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to cholestasis and bile acid accumulation, which leads to the formation of acidic pH and activation of the cellular pathways responsible for tumour growth [4].

Google Scholar, PubMed, and Science direct literature searches were carried out with the above-mentioned keywords, and only the full-text articles were included.

Epidemiology

CCA is a rare malignancy with an overall global incidence of less than 2 in 100000 population. Epidemiological studies indicate that the incidence of cholangiocarcinoma and its subtype varies substantially worldwide [5]. This is partly explained by regional variation in risk factors and differences in genetic backgrounds [1, 5]. CCA is prevalent in northeast Thailand, China, and Korea, where liver flukes are endemic [6]. The incidence in Asia is as high as 100 per 100,000 individuals among men and 50 per 100,000 among women [1]. Though the incidence of CCA in Western countries is low, with an annual incidence of 2.1 cases per 100,000 population, recent epidemiological studies report that the CCA incidence and mortality rates (39%) have increased substantially in the past few decades [7]. The World Health Organization (WHO) database reports a steadily rising incidence of intrahepatic cholangiocarcinoma (i-CCA) and a decreasing or stable incidence of Extrahepatic cholangiocarcinoma (e-CCA) [8]. These trends could be explained by improved diagnostic tools and radiological imaging modalities, changing emigration patterns to Western countries, an increase in the prevalence of chronic liver cell disease, misclassification of Klatskin tumours as an i-CCA, and an increasing laparoscopic cholecystectomy rate which has significantly reduced the prevalence of gallstone disease, an established risk factor for e-CCA rather than i-CCA [7].

Classification

Historically, CCA has been categorised based on location, growth patterns, and histological features. Based on the anatomical location, CCA is generally classified as intrahepatic cholangiocarcinoma-(i-CCA) and Extrahepatic cholangiocarcinoma (e-CCA). e-CCA Itself is classified into perihilar cholangiocarcinoma (p-CCA) / Klatskin tumour and distal (d-CCA). Among these subtypes, p-CCA is the commonest one (60% of CCA), followed by d-CCA (30%) and i-CCA (6-10%) [9].

i-CCA arises within the intrahepatic ducts of the liver parenchyma. p-CCA is the tumour that occurs between the hepatic duct's secondary branches and the cystic duct's insertion. The tumour which arises between the distal insertion of the cystic duct and ampulla of Vater is distal cholangiocarcinoma (d-CCA) [3].

The Bismuth-Corlette classification further subdivides p-CCA based on the proximal extent of biliary involvement into four subtypes (Table 1) [7].

According to the 2019 WHO classification of digestive system tumours, i-CCA is further classified into small duct intrahepatic cholangiocarcinoma (SD-iCCA) and large duct intrahepatic cholangiocarcinoma (LD-iCCA). Mixed hepatocellular Cholangiocarcinoma has also been incorporated as a distinct subtype of cholangiocarcinoma, constituting less than 1% of all liver cancers (9).

Morphologically, by growth patterns, CCA has been categorised as exophytic/mass-forming, periductal-infiltrating, and intraductal/polypoid tumours. Among these growth patterns, mass forming is commonly seen in i-CCA (85%) and peri-ductal-infiltrating growth in p-CCA, while intraductal growth can occur at any location [10].

Histologically, most CCAs are well, moderately, and have poorly differentiated tubular adenocarcinomas (90%). Rarely other histological subtypes are encountered, such as papillary adenocarcinoma, signet-ring carcinoma, squamous cell carcinoma, mucoepidermoid carcinoma, and a lymphoepithelioma-like form [11].

Table - 1-Bismuth-Corlette classification of perihilar cholangio carcinoma [9]

1.	Tumour involves the common hepatic duct below the convergence of the right and left biliary ducts
2.	Tumour involves the hepatic duct convergence but does not extend above the convergence.
3.	Tumour involves the convergence with extension to the right hepatic duct up to second-order ducts
4.	Tumour involves the confluence with extension to the left hepatic duct up to second-order ducts.
5.	Tumours extend into both the right and left hepatic bile ducts

Risk factors

Though most diagnosed Cholangiocarcinoma arises de nova, with no identifiable risk factors. Extensive population-based studies have revealed several well-described risk factors for CCA [2]. Cirrhosis, viral hepatitis C and B, and Hepatolithiasis have been recognised as risk factors for i-CCA [10]. Around 7% of patients with hepatolithiasis develop CCA [2,10]. Primary sclerosing cholangitis (PSC) is an autoimmune disease resulting from intrahepatic and extrahepatic bile duct inflammation and stricture. It is a well-known risk factor for CCA, especially for p-CCA, with a lifetime incidence of 6-36% [5].

Inflammatory bowel disease, obesity, diabetes, bile duct adenomas, previous biliary-enteric bypass, heavy alcohol use, smoking, and exposure to chemical agents (1,2 dichloropropane, dichloromethane, and thorotrast) and radionuclides are some of the other risk factors that have been implicated in the development of CCA [10]. Also, some genetic disorders, such as Lynch syndrome, BAP1 tumour predisposition syndrome, cystic fibrosis, and biliary papillomatosis, are associated with a high risk of progressing into CCA [11].

Clinical presentation

The clinical presentation of CCA depends on the anatomical location of the tumour. The patient with the p-CCA and d-CCA classically presents with the sequelae of biliary obstruction, such as painless jaundice, pale stools, dark urine, and pruritus [11]. i-CCA is often diagnosed incidentally in 20- 25% of patients [12]. Individuals with CCAs often present asymptomatically during early disease stages and become symptomatic at the advanced stage of disease progression. When they do present with symptoms, they usually have unspecific symptoms such as right upper quadrant discomfort, constant dull ache pain in the right hypochondrium (30%), malaise, unexplained weight loss (35%), fever (10%), night sweat and less frequently acute Cholangitis (10%) [13].

On the physical examination, jaundice (90%), hepatomegaly (25%- 40%), right hypochondriac tumour mass (10%), or a rarely distended gallbladder (Courvoisier law) can be observed [14].

Diagnosis and staging

CCA is a “silent killer” partly due to the difficulty in diagnosis before the advanced or metastatic stage [1]. The diagnosis of ÇCA requires a high index of suspicion and a multidisciplinary approach that involves clinical findings, biochemical markers, radiographic images, and histological findings.

Clinically, Cholestasis, abdominal pain, and unexplained weight loss together should always raise suspicion of a hepatobiliary malignancy [15].

Laboratory findings include altered liver function tests and increased tumour marker levels. Liver function tests typically suggest evidence of cholestasis, elevations in total and direct bilirubin, alkaline phosphatase, and gamma-glutamyl transferase [14]. Aspartate aminotransferase and alanine aminotransferase may be normal in the initial stage. In the later stage, there will be an increased level of aminotransferase because of Persistent biliary obstruction. An increase in prothrombin time was also noted, as well as prolonged biliary obstruction due to reduced fat-soluble vitamin absorption. In advanced cases, non-specific markers of malignancy such as albumin, erythrocyte sedimentation rate, c-reactive protein and haemoglobin level can be altered [13].

The value of tumour markers in the diagnosis of CCAs remains controversial. Carbohydrate antigen 19-9

(CA 19-9) and Carcinoembryonic antigen (CEA) are the most used tumour markers [14]. Though both tumour markers are elevated in CCA, they also can be elevated in other cancers (e.g., Cancers of the pancreas, stomach, colon, and gynaecological malignancies), cholestasis in the absence of liver malignancy, bacterial cholangitis and following liver injury. Therefore, measurements of these tumour makers should not be used alone for diagnosing CCA [16]. The sensitivity and specificity for CA 19-9 range from 33 to 93% and 67 to 98%, respectively [17]. Various cut-off values of CA 19-9 have been recommended to diagnose CCA. In unexplained biliary disease, in the absence of chronic inflammatory reaction, and patients with PSC, the cut-off value of CA 19-9 levels of 129 UI/ml and 180 UI/ml are considered suspicious for CCA, respectively [17]. A value higher than 1000 U/mL is compatible with the advanced stage of CCA, often involving the peritoneum [1]. CA-125, CA-195, CA-242, DU-PAN-2, IL-6, and trypsinogen-2 are the other tumour markers which can be increased in CCAs [14].

Radiological investigations are necessary to assess the extent of local-regional or distant spread, staging, and resectability in patients with CCA [1]. An abdominal ultrasound is the first line of investigation to evaluate a patient with jaundice. Though the sensitivity of ultrasound in detecting CCA is low, it helps to demonstrate the level of biliary obstruction or common biliary duct dilatation and exclude benign lesions (e.g., gallstones). Diagnosis of CCA should be suspected when intrahepatic (>8mm), but not extrahepatic, ducts are dilated without stones. [13]. A colour Doppler ultrasound scan accurately predicts portal venous or hepatic artery invasion and resectability. The sensitivity and specificity of the Doppler USS are 93% and 99%, respectively [15].

CT is considered the standard imaging modality for the preoperative assessment of both i-CCA and p-CCA, as it provides a complete assessment of the primary tumour and its relationship with adjacent structures. MRI scans have accuracy similar to CT scans [15]. The investigation of choice to evaluate suspected CCA is cholangiography. It can be percutaneous transhepatic cholangiogram (PTC), endoscopic retrograde cholangiopancreatography (ERCP), or magnetic resonance cholangiopancreatography (MRCP) [18]. ERCP helps to visualise the anatomy of the biliary system and a cytological diagnosis through needle biopsy, biliary brush cytology, and stent insertion for palliative care in unrespectable tumours. MRCP is a non-invasive technique which helps determine the extent of duct involvement. Endoscopic ultrasound, Positron emission tomography with [18F]-2-deoxy-D-glucose, intraductal US, and endoscopic/percutaneous flexible cholangioscopy are some of the new diagnostic techniques under evaluation. [16].

Once cholangiocarcinoma is diagnosed, staging investigations must be performed to screen out the metastatic involvement to other sites because 50% and 10-20% of patients are presented with lymph node-positive and have peritoneal involvement at the initial evaluation. For that, chest radiography, CT abdomen and staging laparoscopy can be performed [14].

Management

Resectable CCAs

Surgical Management

The standard curative treatment for CCA is surgical resection. The goal is to remove the tumour, grossly and microscopically termed R0 resection, while preserving adequate liver function, associated with a high survival rate and low recurrence rate [18]. A "safe" liver resection should leave an FLR of at least 25%. In comparison, an FLR of at least 30% to 40% needs to be considered in livers affected by steatosis, chronic cholestasis, cirrhosis or treated with chemotherapy [17]. Portal vein embolisation can be done in case of inadequate FLR to allow liver remnant hypertrophy [19].

Though resection is indicated for i-CCA and p-CCA, only 15% of patients with i-CCA are candidates for liver resection due to the late presentation in advanced stages. Resectability depends on the location of the tumour lesion in relation to vascular and biliary structures and the quantity and quality of the liver parenchyma after resection [20]. Preoperative assessment is required, and Staging laparoscopy is recommended before

the resection to assess the resectability, especially in patients with high CA 19-9 and significant vascular invasion [21].

R0 resection for p-CCA comprises extended hemi-hepatectomy and extrahepatic bile duct resection. Similarly, resection of i-CCA consists of extended hemi-hepatectomy. Though the presence of lymph node metastasis decreases the outcome of surgery due to high recurrence, there is insufficient data for routine lymph node dissection in CCA management. Still, it is being used for prognostic staging [22]. A recent consensus statement recommended regional lymphadenectomy as a standard part of surgical therapy for i-CCA [23].

Nevertheless, it's important to note that opinions on the benefits of lymph node dissection vary, with some studies suggesting that aggressive lymphadenectomy might not significantly benefit lymph node metastasis [24]. In contrast, others have found no survival difference in patients with negative lymph node metastasis regarding lymph node dissection [25]. Due to this lack of consensus, clinical trials are encouraged to evaluate further the practice of routine lymph node dissection in this area.

Before the surgery, procedures like preoperative biliary drainage (PBD) and portal vein embolisation might be required in a few cases, like obstructive cholangitis and jaundice, to prevent postoperative liver failure. Several studies suggested the benefit of preoperative biliary drainage in jaundiced patients to prevent postoperative complications [26]. The need for PBD would be weighed with the risk of developing cholangitis and septic complications [27]. In some cases, neoadjuvant chemotherapy with gemcitabine and cisplatin is given preoperatively, but still, the benefit is unclear.

Survival after curative intent resection ranges between 25%−40% at five years [28]. However, recurrence remains high at 50%-70%, mainly in the remnant liver. Usually, repeat resection is performed, which is associated with improved survival of 26.1 months compared to 9.6 in patients treated with chemotherapy and 18.6 in patients treated with LRT [29].

Unresectable tumours

Locoregional therapy

Most patients with cholangiocarcinoma present with advanced disease and are not eligible candidates for surgical resection. When surgical resection is impossible, locoregional therapies may be considered as a bridging treatment option to delay or downstage the disease progression and prolong life. Table 2 shows the criteria for nonresectable CCA [30].

Table - 2 - Criteria for unresectable tumours

Hepatic duct involvement up to secondary biliary radicals bilaterally
Encasement or occlusion of the main portal vein proximal to its bifurcation
Atrophy of 1 hepatic lobe with encasement of contralateral portal vein branch
Atrophy of 1 hepatic lobe with contralateral involvement of secondary biliary radicals
Distant metastases (peritoneum, liver, lung)

A large-scale observational study conducted by Park et al. reported that the overall survival period was a median of 3.9 months for patients who did not undergo palliative surgery, chemotherapy, or radiotherapy. Thus, Early implementation of supportive care and active symptom control is important in patients with advanced, recurrent or metastatic disease to improve the patient's quality of life and extend survival. Transarterial chemoembolisation (TACE), drug-eluting bead transarterial chemoembolisation (DEB-TACE), radiofrequency ablation (RFA), microwave ablation (MWA), transarterial radioembolisation (Yttrium90; TARE) are some of the safe and effective locoregional therapy for a patient with i-CCA [31].

RFA has been widely suggested to carry a survival benefit in small, solitary i-CCA or patients with local recurrence or residual tumours after curative surgery. An analysis of 12 studies conducted among 298 patients treated with radioembolisation showed a median overall survival rate of 15.5 months with a 28% response rate [32].

Systemic chemotherapy

Systemic chemotherapy is the initial choice of therapy for at least 3-4 months, followed by locoregional therapy for locally advanced CCA compared with best supportive care [33]. The recommended 1st line of chemotherapy combines cisplatin and gemcitabine [34]. Fluoropyrimidines or oxaliplatin are alternative pharmacological agents. Oxaliplatin can be used in patients with impaired renal function instead of cisplatin [35]. Reassessment of down-staged tumours must be performed following the chemo or radiotherapy to assess the resectability.

Liver transplant

A liver transplant (LT) is reserved for unresectable CCA with no evidence of extrahepatic disease to avoid R1 resection and an inadequate FLR. In the past, LT was not recommended due to poor outcomes. A meta-analysis done in 2000 showed a recurrence of 51% with LT [36]. However, recent studies show satisfying results of LT in combination with neoadjuvant chemotherapy, contradicting the past.

In their prospective case series, Keri E Lunsford et al. enrolled patients who underwent at least six months of chemotherapy. They concluded that patients with pre-transplant disease stability on neoadjuvant therapy benefit from liver transplantation with promising results of 83% OS rate at five years [37]. Also, an international retrospective study with 2301 patients reported a 5-year OS of 65% for very early i-CCA (single tumour <2cm) and 45% for advanced iCCA (single tumour> 2cm or multifocal disease). Similarly, the recurrence rate was 18% in early i-CCA versus 65% in advanced i-CCA [38].

Similarly, the concerns of LT for p-CCA also charged favourably. Sarwa Darwish Murad et al., included 216 patients with pCCA who underwent neoadjuvant chemoradiotherapy followed by LT to determine LT's effectiveness [38]. The study concluded that neoadjuvant followed by LT was highly effective, with 65% of recurrence-free survival after five years. A comparative study with 71 patients also suggested LT with neoadjuvant chemoradiation offers a better survival rate of 82% and less recurrence when compared to resection (13 vs 27) [39].

In summary, the view of LT in the management of CC has been changed, and further research in this area is encouraged, considering the tumour stability and neoadjuvant protocols.

Supportive care

Biliary drainage is considered for obstructive jaundice patients with unresectable or metastatic CCA to alleviate obstructive symptoms such as pruritus and persistent jaundice and to improve liver and renal dysfunction [37]. The decision to perform biliary drainage should be made in a multidisciplinary team setting because improper biliary drainage may cause infective complications and, eventually, resectable patients to become unresectable [38].

Patients with cholangitis or sepsis originating from the biliary tract, intractable pruritus, persistent and severe jaundice with a total serum bilirubin level of more than15 mg/dl and patients who are eligible for neoadjuvant chemotherapy or preoperative procedures such as portal embolisation are the absolute indication for the biliary drainage [40].

The commonly used modality for biliary drainage is non-surgical stenting methods such as ERCP, PTC and surgical bypass. Endoscopic biliary stenting is the most common method, and If the endoscopic stenting is not practicable, Percutaneous transhepatic biliary drainage (PTC) is recommended [41]. Surgical bypass can be considered in patients with unresectable CCA at the time of exploration, who cannot undergo repeat endoscopic or percutaneous stent exchanges and those with a well-estimated life expectancy and fit for surgery. The stents can either be self-expanding metallic or plastic (polyethylene) stents. Metal stents are more expensive than plastic stents. But have larger diameters and provide better patency rates. And plastic stents need to be changed. Studies conducted in past decades reported that a metal stent is desired in patients with a life expectancy of more than five months because it is cost-effective and needs fewer interventions with shorter hospitalisations [42].

References

1. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2018 Feb;15(2):95-111. doi: 10.1038/nrclinonc.2017.157. Epub 2017 Oct 10. PMID: 28994423; PMCID: PMC5819599.

2. Gupta A, Dixon E. Epidemiology and risk factors: intrahepatic cholangiocarcinoma. Hepatobiliary Surg Nutr. 2017 Apr;6(2):101-104. doi: 10.21037/hbsn.2017.01.02. PMID: 28503557; PMCID: PMC5411279.

3. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet. 2014 Jun 21;383(9935):2168-79. doi: 10.1016/S0140-6736(13)61903-0. Epub 2014 Feb 26. PMID: 24581682; PMCID: PMC4069226.

4. Labib, P.L., Goodchild, G. & Pereira, S.P. Molecular Pathogenesis of Cholangiocarcinoma. BMC Cancer 19, 185 (2019). https://doi.org/10.1186/s12885-019-5391-0

5. Kirstein MM, Vogel A. Epidemiology and Risk Factors of Cholangiocarcinoma. Visc Med. 2016 Dec;32(6):395-400. doi: 10.1159/000453013. Epub 2016 Dec 1. Erratum in: Visc Med. 2017 Jun;33(3):226. PMID: 28229073; PMCID: PMC5290446.

6. Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D; ESMO Guidelines Committee. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016 Sep;27(suppl 5):v28-v37. doi: 10.1093/annonc/mdw324. PMID: 27664259.

7. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet. 2014 Jun 21;383(9935):2168-79. doi: 10.1016/S0140-6736(13)61903-0. Epub 2014 Feb 26. PMID: 24581682; PMCID: PMC4069226.

8. Patel, T. Worldwide trends in mortality from biliary tract malignancies. BMC Cancer 2, 10 (2002). https://doi.org/10.1186/1471-2407-2-10

9. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020 Jan;76(2):182-188. doi: 10.1111/his.13975. Epub 2019 Nov 13. PMID: 31433515; PMCID: PMC7003895.

10. Suarez-Munoz MA, Fernandez-Aguilar JL, Sanchez-Perez B, Perez-Daga JA, Garcia-Albiach B, Pulido-Roa Y, Marin-Camero N, Santoyo-Santoyo J. Risk factors and classifications of hilar cholangiocarcinoma. World J Gastrointest Oncol. 2013 Jul 15;5(7):132-8. doi: 10.4251/wjgo.v5.i7.132. PMID: 23919107; PMCID: PMC3731526.

11. Nakanuma Y, Sato Y, Harada K, Sasaki M, Xu J, Ikeda H. Pathological classification of intrahepatic cholangiocarcinoma based on a new concept. World J Hepatol 2010; 2: 419–27.

12. Watanapa P, Watanapa WB. Liver fluke-associated cholangiocarcinoma. Br J Surg 2002;89:962-70. DOI PubMed

13. Grainge MJ, West J, Solaymani-Dodaran M, Aithal GP, Card TR. The antecedents of biliary cancer: a primary care case-control study in the United Kingdom. Br J Cancer 2009;100:178–180.

14. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 2011;8:512-22. DOI PubMed PMC

15. Welzel TM, Mellemkjaer L, Gloria G, Sakoda LC, Hsing AW, El Ghormli L, et al. Risk factors for intrahepatic cholangiocarcinoma in a low-risk population: a nationwide case-control study. Int J Cancer 2007;120: 638–641.

16. Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. Hepatology 2011;54:463-71. DOI PubMed PMC DOI: 10.1159/000077991

17. Elvevi A, Laffusa A, Scaravaglio M, Rossi RE, Longarini R, Stagno AM, Cristoferi L, Ciaccio

A, Cortinovis DL, Invernizzi P, Massironi S. Clinical treatment of cholangiocarcinoma: an updated comprehensive review. Ann Hepatol. 2022 Sep-Oct;27(5):100737. doi: 10.1016/j.aohep.2022.100737. Epub 2022 Jul 7. PMID: 35809836

18. Higuchi R, Ota T, Araida T, Kobayashi M, Furukawa T, Yamamoto M. Prognostic relevance of ductal margins in operative resection of bile duct cancer. Surgery. 2010 Jul;148(1):7-14. doi: 10.1016/j.surg.2009.11.018. Epub 2010 Feb 8. PMID: 20116818.

19. Shoup M, Gonen M, D'Angelica M, Jarnagin WR, DeMatteo RP, Schwartz LH, Tuorto S, Blumgart LH, Fong Y. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. J Gastrointest Surg. 2003 Mar-Apr;7(3):325-30. doi: 10.1016/s1091-255x(02)00370-0. PMID: 12654556.

20. Chapelle T, Op de Beeck B, Roeyen G, Bracke B, Hartman V, De Greef K, Huyghe I, Van der Zijden T, Morrison S, Francque S, Ysebaert D. Measuring future liver remnant function prior to hepatectomy may guide the indication for portal vein occlusion and avoid posthepatectomy liver failure: a prospective interventional study. HPB (Oxford). 2017 Feb;19(2):108-117. doi: 10.1016/j.hpb.2016.11.005. Epub 2016 Dec 9. PMID: 27956027.

21. Zori AG, Yang D, Draganov PV, Cabrera R. Advances in the management of cholangiocarcinoma. World J Hepatol. 2021 Sep 27;13(9):1003-1018. doi: 10.4254/wjh.v13.i9.1003. PMID: 34630871; PMCID: PMC8473501.

22. Bird N, Elmasry M, Jones R, Elniel M, Kelly M, Palmer D, Fenwick S, Poston G, Malik H. Role of staging laparoscopy in the stratification of patients with perihilar cholangiocarcinoma. Br J Surg. 2017 Mar;104(4):418-425. doi: 10.1002/bjs.10399. Epub 2016 Nov 8. PMID: 27861766.

23. Kambakamba P, Linecker M, Slankamenac K, DeOliveira ML. Lymph node dissection in resectable perihilar cholangiocarcinoma: a systematic review. Am J Surg. 2015 Oct;210(4):694-701. doi: 10.1016/j.amjsurg.2015.05.015. Epub 2015 Jun 29. PMID: 26212390.

24. Navarro JG, Lee JH, Kang I, Rho SY, Choi GH, Han DH, Kim KS, Choi JS. Prognostic significance of and risk prediction model for lymph node metastasis in resectable intrahepatic cholangiocarcinoma: do all require lymph node dissection? HPB (Oxford). 2020 Oct;22(10):1411-1419. doi: 10.1016/j.hpb.2020.01.009. Epub 2020 Feb 8. PMID: 32046923

25. Sahani D, Prasad SR, Tannabe KK, Hahn PF, Mueller PR, Saini S. Thorotrast-induced cholangiocarcinoma: case report. Abdom Imaging 2003;28:72-4. DOI PubMed

26. McGee EE, Jackson SS, Petrick JL, et al. Smoking, alcohol, and biliary tract cancer risk: a pooling project of 26 prospective studies. J Natl Cancer Inst 2019;111:1263-78. DOI PubMed PMC

27. Kubo S, Kinoshita M, Takemura S, et al. Characteristics of printing company workers newly diagnosed with occupational cholangiocarcinoma. J Hepatobiliary Pancreat Sci 2014;21:809-17. DOI PubMed

28. Mecklin JP, Järvinen HJ, Virolainen M. The association between cholangiocarcinoma and hereditary nonpolyposis colorectal carcinoma. Cancer 1992;69:1112-4. DOI PubMed

29. Li DY, Zhang HB, Yang N, Quan Y, Yang GS. Routine lymph node dissection may be not suitable for all intrahepatic cholangiocarcinoma patients: results of a monocentric series. World J Gastroenterol. 2013 Dec 21;19(47):9084-91. doi: 10.3748/wjg.v19.i47.9084. PMID: 24379635; PMCID: PMC3870563

30. Iacono C, Ruzzenente A, Campagnaro T, Bortolasi L, Valdegamberi A, Guglielmi A. Role of preoperative biliary drainage in jaundiced patients who are candidates for pancreatoduodenectomy or hepatic resection: highlights and drawbacks. Ann Surg. 2013 Feb;257(2):191-204. doi: 10.1097/SLA.0b013e31826f4b0e. PMID: 23013805.

31. Ebata T, Mizuno T, Yokoyama Y, Igami T, Sugawara G, Nagino M. Surgical resection for Bismuth type IV perihilar cholangiocarcinoma. Br J Surg. 2018 Jun;105(7):829-838. doi: 10.1002/bjs.10556. Epub 2017 May 10. PMID: 28488733

32. KN, Gores GJ. Cholangiocarcinoma. Gastroenterology. 2005 May;128(6):1655-67. doi: 10.1053/j.gastro.2005.03.040. Erratum in: Gastroenterology. 2005 Jul;129(1):400. PMID: 15887157

33. Hewitt DB, Brown ZJ, Pawlik TM. Surgical management of cholangiocarcinoma. Hepatoma Res 2021;7:75.

34. Lunsford KE, Javle M, Heyne K, Shroff RT, Abdel-Wahab R, Gupta N, Mobley CM, Saharia A, Victor DW, Nguyen DT, Graviss EA, Kaseb AO, McFadden RS, Aloia TA, Conrad C, Li XC, Monsour HP, Gaber AO, Vauthey JN, Ghobrial RM; Methodist–MD Anderson Joint Cholangiocarcinoma Collaborative Committee (MMAJCCC). Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. Lancet Gastroenterol Hepatol. 2018 May;3(5):337-348. doi: 10.1016/S2468-1253(18)30045-1. Epub 2018 Mar 13. Erratum in: Lancet Gastroenterol Hepatol. 2018 Jun;3(6):e3. PMID: 29548617.

35. Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, Vibert E, Cherqui D, Grant DR, Hernandez-Alejandro R, Dale CH, Cucchetti A, Pinna A, Hwang S, Lee SG, Agopian VG, Busuttil RW, Rizvi S, Heimbach JK, Montenovo M, Reyes J, Cesaretti M, Soubrane O, Reichman T, Seal J, Kim PT, Klintmalm G, Sposito C, Mazzaferro V, Dutkowski P, Clavien PA, Toso C, Majno P, Kneteman N, Saunders C, Bruix J; iCCA International Consortium. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment. Hepatology. 2016 Oct;64(4):1178-88. doi: 10.1002/hep.28744. Epub 2016 Aug 24. PMID: 27481548.

36. Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, Botha JF, Mezrich JD, Chapman WC, Schwartz JJ, Hong JC, Emond JC, Jeon H, Rosen CB, Gores GJ, Heimbach JK. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology. 2012 Jul;143(1):88-98.e3; quiz e14. doi: 10.1053/j.gastro.2012.04.008. Epub 2012 Apr 12. PMID: 22504095; PMCID: PMC3846443.

37. Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, Gores GJ, Nagorney DM. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg. 2005 Sep;242(3):451-8; discussion 458-61. doi: 10.1097/01.sla.0000179678.13285.fa. PMID: 16135931; PMCID: PMC1357753.

38. Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB, Rosen CB. Liver transplantation for unresectable perihilar cholangiocarcinoma. Semin Liver Dis. 2004 May;24(2):201-7. doi: 10.1055/s-2004-828896. PMID: 15192792.

39. Sharma A, Dwary AD, Mohanti BK et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. J Clin Oncol 2010; 28: 4581–4586.

40. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273–81.

41. Okusaka T, Nakachi K, Fukutomi A et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer 2010; 103: 469–474.

42. Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. Gastrointest Endosc 2006;63:986–995.