REVIEW ARTICLE

Cholangiocarcinoma: State of the Art

Bobak Moazzami[1] · Keivan Majidzadeh-A[2] · Arash Dooghaie-Moghadam[1] · Pegah Eslami[3] ·
Niloofar Razavi-Khorasani[1] · Shahrokh Iravani[2] · Alireza Khoshdel[2] · Farhad Shahi[1] · Habibolah Dashti[1] ·
Azim Mehrvar[2] · Mohssen Nassiri Toosi[1]

Abstract
Background Cholangiocarcinoma (CCA) is the second most frequent primary liver tumor and defined as the heterogeneous group of tumors derived from cells in the biliary tree.
Methods and Results Based on the anatomical locations (intrahepatic, perihilar, and distal), there are various approaches to the diagnosis and treatment of CCA. Imaging modalities, staging classifications, understandings around natural behavior of CCA, and therapeutic strategies have had remarkable progress in recent years.
Conclusions This article reviews and discusses the epidemiology, clinical presentation, diagnosis, and treatment modalities of CCA; determines the appropriate inclusion and exclusion criteria for liver transplantation (LT); and defines the risk of disease progression for patients in the waiting list of LT.

Keywords Cholangiocarcinoma · Hepatectomy · Liver surgery · Liver transplantation · Neoadjuvant therapy

Introduction

Cholangiocarcinoma (CCA) is the heterogeneous group of tumors derived from cells of the bile ducts and exhibit biliary epithelial differentiation [1]. Anatomically, the disease can be classified into three categories: intrahepatic cholangiocarcinoma (iCCA), hilar CCA, and distal CCA. iCCA arising from proximal to the second-degree bile ducts, hilar CCA is localized between the second-degree bile ducts and the cystic duct, and distal CCA originates distal to the cystic duct [1–3]. Although, no specific risk factor has been identified for development of CCA, most cases are sporadic and the underlying etiology is unknown. However, several studies have suggested that chronic biliary inflammation and increased cellular turnover, liver cirrhosis, chronic hepatitis B and C infection, diabetes, obesity, and excess use of alcohol have been linked to higher risks of developing CCA [4]. The diagnosis of CCA is mainly made by both clinical and imaging findings, and whenever the diagnosis of CCA is confirmed, staging of the disease severity is needed to assess the degree of extension of tumor outside the liver and biliary tree [1, 4]. Herein, we aimed to review the epidemiology, clinical presentation, and therapeutic strategies of CCA, and highlight the CCA in the liver transplantation (LT) setting.

Epidemiology of Cholangiocarcinoma

Approximately, 13% of overall cancer-related mortality is due to hepatobiliary malignancies. In this context, CCA accounts for about 15–20% of the primary hepatobiliary malignancies, which makes it the second most common primary liver tumor [5–8]. The incidence of CCA seems to be increasing, and it is the leading cause of nearly 20% of the deaths from hepatobiliary cancers [5]. The underlying reason for the increasing trend in CCA incidence has not been fully understood so far. Epidemiological studies showed that men have 1.5 fold increased risk of CCA development when compared with women. Moreover, the incidence of CCA is more commonly occurred after the fourth decade of life except for

✉ Azim Mehrvar
  ltrc.tehran@gmail.com

✉ Mohssen Nassiri Toosi
  nasirito@sina.tums.ac.ir

1 Liver Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran

2 Research Center for Cancer Screening and Epidemiology, AJA University of Medical Sciences, Tehran, Iran

3 Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

patients with primary sclerosing cholangitis which can present the disease earlier [7, 9, 10].

Classification of CCA

Most commonly, CCA is classified into three groups of intrahepatic (IH-CCA or iCCA), perihilar (pCCA), and distal (dCCA) subtypes which is based on the anatomical location of CCA. pCCA, which is also called Klatskin, and dCCA were previously grouped as extrahepatic CCA (EH-CCA) due to the differences in their tumor biology and management [7, 11].

Clinical Presentation and Diagnosis of Cholangiocarcinoma

The clinical presentation of CCA is often subtle and may manifest without any evident signs and symptoms. In some cases, the manifestation of CCA may cause jaundice as well as non-specific symptoms such as weight loss, night sweets, abdominal pain, emesis, vomiting, loss of appetite, and also the increase of cholestasis related parameters such as alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and Bilirubin [12, 13]. Diagnosis of CCA is by the combination of the clinical presentation, imaging information, and biopsy modalities [7].

Diagnosing the Source of Jaundice

As stated above, jaundice and particularly painless jaundice is one the common presentations of CCA [4, 7]. Generally, the increase of the conjugated bilirubin can be due to the obstruction of biliary ducts that lead to the presence of acholia/pale stools, or it can have intrahepatic (i.e., hepatocellular damage) causes, which acholia does not usually develop (except in the first weeks of acute hepatitis) [14].

Initial Investigations

To determine the source of jaundice, physical examination and blood tests including full liver function should be performed prior to the imaging and other investigations. Generally, the increase of ALP, GGT, bile salts, 5'nucleotidase, or cholesterol is expected but hepatocyte enzymes such as AST are expected to be less elevated [4].

Diagnosis

Currently, there is no standard diagnostic tool for early detection of CCA and therefore could result in longer diagnostic delay and

higher morbidity and mortality [15, 16]. Symptoms often developed at advanced stage disease and compared to nonsymptomatic patients; symptomatic patients have a lower chance of tumor resection [17, 18]. Less than half of CCA cases are diagnosed incidentally, for example, by cross-sectional imaging performed for other reasons [2, 17]. Imaging modalities such as ultrasound (US), contrast-enhanced ultrasound (CEUS), computed tomography (CT), magnetic resonance imaging (MRI) and Fludeoxyglucose-positron emission tomography (18FDG-PET) also play a crucial role in other stages of managing such as staging, follow-up, and monitoring the response to the therapy. Studies also show non-morphologic imaging as a potential tool for the prediction of the disease prognosis [19–21].

Tumor Markers

Carbohydrate antigen 19–9 (CA 19–9) is the most commonly used tumor marker for CCA and distinguishing CCA from HCC. Although CA 19–9 is more specific than other tumor markers such as CEA and CA-125, it is elevated in benign cholangiopathies or gastrointestinal, pancreatic, and gynecologic malignancies other than CCA. Also, Lewis antigen-negative patients do not express CA 19–9 [7].

Role of Ultrasound for CCA Detection

Although the unenhanced US lacks specific features, it is one of the primary diagnostic tools that shows a high detection rate. Also, CEUS, which is generally used in the setting of chronic liver disease, has a possibility of misclassification between iCCA and HCC in the use of unenhanced US [4, 22, 23] .On the other hand, dCCA is diagnosed with a high accuracy rate of 80–95%, but pCCA is more difficult to identify using the US. Generally, in patients with jaundice which the benign causes for the obstruction of the bile duct are excluded [24]. SpyGlass®, which is a novel endoscopic technique, is suggested as a more sensitive technique for the detection of CCA than other standard endoscopic techniques [25–27].

Role of Computed Tomography Imaging

Currently, the standard radiologic assessment for characterization and staging of CCA is CT [28]. The imaging patterns of iCCA in cirrhotic patients displayed as an arterial peripheral-rim enhancement with progressive homogeneous contrast uptake until the delayed or stable contrast uptake through the different dynamic phases [29]. Moreover, additional findings such as capsular retraction, delayed enhancement, satellite nodules, and vascular invasion are mainly supportive of iCCA diagnosis. In some cases that the tumor lesion is smaller than 1 cm, the characterization is challenging specially in in the presence of cirrhosis or atypical features [30]. Also, CT

findings can be used in preoperative evaluation of patients' prognosis, estimation of the resectability of pCCA, and assessment of the involvement of portal vein, hepatic artery, and bile ducts [31]. However, it is less accurate in the identification of lymph nodes and distant metastases [32].

Role of Magnetic Resonance and Other Imaging

Similar to CT, MRI is used in the diagnosis and staging of CCA and could help clinicians in estimation of the respectability of pCCA, and evaluation of the involvement of portal vein and bile ducts [29, 32]. On the other hand, the use of hepato-specific contrast media and diffusion-weighted imaging (DWI) is one of the MRI advantages which are helpful in the discrimination of HCC and iCCA [33]. For the investigation of distant metastasis or nodal metastases, and completing the disease staging, the best modality is 18FDG-PET imagining [4].

Invasive Techniques for Confirmatory Tissue Diagnosis

A biopsy is required to confirm CCA diagnosis, which is minimally invasive in the diagnosis of iCCA and pCCA and mainly performed percutaneously with guiding of US imaging [4, 34]. Studies indicate that employing CEUS imaging increases the accuracy of the liver biopsy compared to the US [4]. The histological diagnosis of iCCA is according to the WHO classification of biliary tract cancer that could be differentiated into two main categories such as adenocarcinoma and mucinous carcinoma [35]. The tubular and/or papillary structures and a variable fibrous stroma are the most common histological findings of an iCCA [36].

Staging Systems of Cholangiocarcinoma

Staging is required to establish a systematic approach to prognostication, therapeutic stratification, and outcome comparison. So far, there are three major staging systems for iCCA including the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC), the National Cancer Center of Japan (NCCN) staging systems, and the Liver Cancer Study Group of Japan (LCSGJ). The AJCC/UICC has shown stage-survival correlation. Generally, cancer itself is staged as a primary tumor (T), regional lymph nodes metastasis (N), and the presence of distant metastases (M). This TNM classification is broadly used in oncology [37].

Therapeutic Strategies for Cholangiocarcinoma

Hepatic Surgery

Although the diagnosis of CCA is made at the late stages in the majority of the cases, the only possible curative option is surgical treatment [18, 38]. On the other hand, in cases with distant metastases, bilateral, multifocal disease, and comorbidities associated with operative risks, surgical resection is not recommended [7]. Also, studies showed that uncorrected preoperative jaundice can be associated with some of the postoperative complications. In the cases of CCA, major postoperative complications are intra-abdominal abscesses, biliary fistulae, sepsis, and bile duct leaks [7, 39, 40].

Nonsurgical Therapies

Various chemotherapy approaches have been proposed for the treatment of CCA patients. Two phase III randomized controlled trials have shown a better outcome and survival rate of CCA patients with combination of gemcitabine/cisplatin therapy when compared to gemcitabine monotherapy and also erlotinib plus gemcitabine/cisplatin compared to gemcitabine/cisplatin, respectively [41, 42]. Other therapeutic methods include radiofrequency ablation, hepatic arterial infusion chemotherapy (HAI), transarterial chemoembolization (TACE), drug-eluting bead-TACE, radioembolization, stereotactic radiotherapy, photodynamic therapy (PDT), and proton beam therapy (PBT) [7, 43–45].

First Line Medical Therapy

Most cases of cholangiocarcinoma are unresectable resulting in a poor prognosis. Historically, CCA is considered as chemotherapy-resistant cancer. However, clinical trials have shown that systemic chemotherapy greatly extended the survival of patients with advance CCA. Thus, systemic chemotherapy remains the cornerstone of palliative therapy for the majority of unresectable cholangiocarcinoma cases. Although it has been well-established that cancers arising from various anatomic sites of biliary tree have distinct histological phenotype, clinical trials have been grouped together all intrahepatic, perihilar, distal, gall bladder, and ampullary carcinoma and collectively referred them as biliary cancers. Therefore, it becomes difficult to interpret these findings and also limit the generalizability of the results.

Gemcitabine Plus Cisplatin Currently, the first-line treatment for advanced unresectable cholangiocarcinoma is based on the combination of gemcitabine plus platinum. In a study done by Valle et al. in 2010 (also known as UK ABC-02 trial), they conducted a clinical trial of cisplatin and gemcitabine in

patients with advanced CCA. This study included 241 CCA patients from a total of 410 patients who were randomly assigned to receive gemcitabine alone or in combination with cisplatin [46]. The survival rate of patients who received the doublet was significantly higher than gemcitabine alone (HR, 0.64; 95% CI, 0.52–0.80; $P < 0.001$). Results also showed that the combination of gemcitabine and cisplatin was well tolerated with similar adverse events between the two groups. These results were supported by a Japanese randomized trial (BT22 study) showing that gemcitabine plus cisplatin therapy was effective and well tolerated [47].

Other Gemcitabine-Based Regimens Gemcitabine plus S-1 was compared to gemcitabine plus cisplatin in the Japanese phase III FUGA-BT trial [48]. In the preliminary reports, gemcitabine plus S-1 was non-inferior in terms of median overall survival (15.1 versus 13.4 months), median progression-free survival (6.8 versus 5.8 months), and objective response rate (30 versus 32%). Another non-randomized phase II study investigated the substitution of oxaliplatin (GEMOX) for cisplatin as an alternative for standard regiment in patients who are medically unfit to receive cisplatin-based therapy [49]. Findings presented in this study indicated promising results for combination of gemcitabine and oxaliplatin in terms of well tolerability and efficacy. It should be noted that evaluating prognostic factors including gender, disease status, liver metastasis, and number of metastatic sites along with biochemical parameters have been argued to be the most important factors than therapy itself in determining the overall survival outcome [50, 51]. Thus, GEMOX is considered as one of the standard first-line regimens for advanced biliary tract cancer. The combination of gemcitabine plus oxaliplatin (GEMOX) and bevacizumab was also evaluated in a phase II trial [52]. Whether this combination is superior to GEMOX alone or gemcitabine plus cisplatin should be further assessed in larger randomized clinical trials.

Gemcitabine (1000 mg/m2 on days 1 and 8) plus capecitabine (650 mg/m2 twice daily for 14 days of every 21-day cycle) is another gemcitabine base regimen for cholangiocarcinoma. In Knox et al. trial [53], the overall survival rate was reported to be 12.7 months. However, another study conducted by the Southwest Oncology Group (SWOG) reported that the median survival rate was to be only 7 months [54].

Weekly gemcitabine plus nab-paclitaxel combination has been evaluated in a phase II trial for metastatic cholangiocarcinoma with the median overall survival of 12.4 months [55]. Shroff et al.'s [56] phase II study of the combination of gemcitabine, cisplatin, and nab-paclitaxel reported a median progression-free and overall survival rate of 11.8 and 19.2 months, respectively.

Several new cytotoxic agents have also been proposed to possibly enhance the efficacy of chemotherapy treatment. In particular, docetaxel, paclitaxel, and irinotecan have been

added to doublet reference chemotherapy regimen, but the results showed unfavorable outcomes such as lower response rate and disease control rate [57]. An ongoing phase II/III trial named AMEBICA are undertaken to determine whether FOLFIRINOX or in combination with gemcitabine/cisplatin could further improve the outcomes of patients with locally advanced non-resectable or metastatic biliary tract cancer [58].

Patients with Persistent Biliary Obstruction For patients who have persistent hyperbilirubinemia despite stenting, a non-gemcitabine-based regimen, such as fluoropyrimidine plus oxaliplatin, is a good option. In recent studies, FU-based combination therapies may reach a longer overall survival rate but did not seen to be exceeded more than 1 year [59].

Second Line Medical Therapy

Currently, there is no effective second-line treatment in regard to any advantages over best supportive care in a prospective RCT. Therefore, it is still unclear whether administering chemotherapy could benefit patients failing the standard first-line treatment [60–62]. In addition, the rapid deteriorating nature of CCA mostly precludes further evaluation of second-lines of treatment. It is noteworthy that based on small prospective phase II studies, approximately 20–40% of patients are offered an alternative chemotherapy regimen that can benefit highly selected patient populations [19, 63]. In terms of second-line treatment, a fluoropyrimidine-based schedule is considered as the most appropriate regimen in this setting [64]. However, the major limitations in proposing the best second-line treatment option are due to marked heterogeneity across studies as well as poor level of evidence. Thus, future well-designed prospective trials are warranted to elucidate these findings.

Phase III randomized ABC-06 study showed an overall better survival rate of FOLFOX chemotherapy when compared to BSC alone (6.2 vs. 5.3 months). However, although FOLFOX is considered as the standard of treatment following progression on cisplatin/gemcitabine (CisGem), the benefit was modest in Lamarca et al.'s study [65]. Moreover, in preliminary results presented at the 2019 annual American Society of Clinical Oncology (ASCO) meeting, FOLFOX has been shown to be significantly associated with better overall survival outcomes (26% vs 11% for 1 year).

Immunotherapy

One of the biggest breakthroughs in the last decade of cancer research was cancer immunotherapy. The growing body of evidence suggested that immune checkpoints and other T cell coinhibitory pathways could have a significant impact on anti-tumor immune response and increased overall survival rates in patients with various solid organ tumors. The anti-tumor

activity of monoclonal antibodies is based on initiate or inhibit programmed cell death. There have been two major immuno-suppressive pathways to operate against two distinct inhibitory receptors on T cells including programmed death-1 (PD1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) and their specific ligands. These checkpoints are known as negative regulator of immune recognition to prevent excessive inflammation. Phase 1b trial of pembrolizumab monotherapy has been conducted on 89 patients with biliary tract cancer [66]. Thirty-seven patients (42%) who were assessed for PD-L1 expression had positive PD-L1. Twenty-four patients were received pembrolizumab in which 4 patients (17%) developed partial response and 4 (17%) were found to have stable disease. Other studies have shown similar responses in treatment with pembrolizumab among patients with biliary tract cancer and expressing PD-L1 [67, 68]. A phase II clinical trial (NCT03704480) is underway investigating durvalumab (anti-PD-L1) in combination with tremelimumab (anti- CTLA-4) with or without paclitaxel in patients with advanced CCA. The use of immunotherapy for treatment of advanced biliary cancer is on its early stages, and within the following years, our understanding regarding the administration of these agents will substantially increase our knowledge in the management of CCA.

Indication for Liver Transplantation

Liver Transplantation Alone

Orthotopic liver transplantation (OLT) is potentially a promising treatment modality due to its ability to achieve a tumor-free margin and perform a radical resection. In contrast, studies have reported that 5-year survival is only 28% in which the tumor recurs in nearly half of the patient, and the long-term survival is less than 20% [69–71]. The majority of recurrences develop within the first 2 years, and studies showed no association between adjuvant therapy and survival (Goldstein et al. 1993). Therefore, although OLT is an effective treatment for pCCA (with a recurrence-free 5-year survival 68%), OLT is not a recommended option in the treatment of CCA as a monotherapy [71].

Neoadjuvant Therapy and Liver Transplantation

Currently, the consideration for performing LT in patients with iCCA is not recommended mainly due to the lack of evidence and controversial reported outcomes [34]. The unsatisfactory long-term survival outcomes of patients who underwent LT made this procedure useless [72]. Patients who underwent LT alone have a 3-year survival of 50–65% [73]. The concomitant chemotherapies are an essential element in enhancing the survival rate with those who underwent neoadjuvant therapy in

combination with LT often show better long-term survival outcome [74]. Although patients who underwent liver transplantation alone have overall poor results, those with absence of regional lymph node metastases showed better outcome following LT [75]. Despite promising results of local tumor control in the management of iCCA, the complications related to high-dose of brachytherapy are still challenging and attributed to high morbidity and mortality [76].

Prediction of Tumor Recurrence after Orthotopic Liver Transplantation

As mentioned previously, preoperative staging and neoadjuvant chemoradiation treatment in liver transplantation settings may result in an excellent long-term recurrence-free survival in early-stage cases with small hilar CCA [77]. Studies show aggressive tumor biology, perineural invasion, and including multifocality, but not tumor size can be independent predictors of tumor recurrence [74]. It seems a clinical model is still needed to guide the use of OLT and predict its outcomes.

Future Directions

Current clinical trials in the area of CCA are mainly limited by the sample size. Also, dissection of the molecular pathways causing CCA will help in the selection of an individualized medicine approach. On the other hand, there are few studies on evaluation of the therapeutic efficacy of targeted agents combined with retrospective analysis of transcriptomic data, but clinical trials are in favor of targeting EGFR combined with other molecular targets or chemotherapeutics [41]. Other promising approaches include Targeting JAK/STAT3 [78], Inhibition of IDH1/2-mutations [79], Targeting of cancer-associated fibroblasts (CAFs) [80], and targeting FGFR2 [81]. Identification of new and more specific tumor biomarkers is another important future direction [82]. Electrospray ionization tandem mass spectrometry (ESI-MS), surface-enhanced laser desorption, two-dimensional gel electrophoresis or ionization, protein chips, and proteome analysis are other technologies that can be used in the development of new specific diagnostic methods [83].

Conclusions

Therapeutic options for management of CCA are limited and associated with poor outcome and mortality. Despite recent advances in diagnostic modalities of CCA such as imaging and cytopathology techniques, early detection of CCA is still challenging. Clinical diagnosis of CCA is based on radiological evidence of *malignant strictures* of the common *bile duct,* increased serum levels of CA 19–9, malignant-looking

appearance of a lesion during MRI, and normal serum levels of IgG4 level. Liver transplantation in combination with neo-adjuvant chemotherapy has shown to improve overall survival rate among CCA patients.

Compliance with Ethical Standards

Conflict of Interest   The authors declare that they have no competing interests.

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