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Cholangiocarcinoma: A Comprehensive Review and Update Guideline

Kadek Nandita Nugraha[1], Baiq Inna Dwi Hardyningrat[1], Devi Chandra Kirana[1], Najla Aulia Yahya[1], Salsabila Dinda Nuril Ishlahi[1], Shofia Kadarisma[1], Fathul Djannah[2*]

[1] Medical Education Study Program, Faculty of Medicine and Health Sciences, Mataram University, Mataram, Indonesia
[2] Lecturer of Anatomical Pathology Departement, Faculty of Medicine and Health Sciences, Mataram University, Mataram, Indonesia

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Corresponding Author:
Fathul Djannah
fdjannah354@gmail.com

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Abstract: Cholangiocarcinoma is a rare cancer of the gastrointestinal system. However, the prognosis for people with this disease has not improved in the last decade. CCA has a poor prognosis because most cases are diagnosed at an advanced stage and the availability of treatment options is limited. This literature review aims to provide information regarding the current understanding and guidelines for cholangiocarcinoma. In this literature review, we searched the National Center for Biotechnology Information (NCBI) and Google Scholar using the search keywords "Cholangiocarcinoma", "cholangiocarcinoma management", "cholangiocarcinoma guidelines" taken ScienceDirect, Researchgate, National Comprehensive Cancer Network, and PubMed published in the last 10 years. From various databases, the literature used and according to the selection criteria amounted to 50 articles In the latest articles and the Cancers NCCN Guidelines for Biliary Tract Cancer in 2023, CCA treatment is carried out based on the patient's profile. Targeted therapy is an additional treatment option today by targeting the molecular profile involved in the pathogenesis of CCA. The diagnosis of cholangiocarcinoma is made through histology, radiography, and laboratory examination. Based on the Cancers NCCN Guidelines for Biliary Tract Cancer in 2023, the treatment carried out consists of determining cancer staging, surgery, radiation therapy, and systemic therapy.

Keywords: Cholangiocarcinoma; Guideline cholangiocarcinoma; Management cholangiocarcinoma

Introduction

The incidence of CCA is indeed lower than other cancers. Of all cases of gastrointestinal cancer, CCA only occurs in about 3-5% (Qurashi et al., 2023). The incidence and mortality of CCA worldwide vary widely due to genetic and geographic risk factors (Khan et al., 2019). In the last decade, intrahepatic CCA has experienced an increase in mortality in several regions, such as Ireland and the UK with 2 cases per 100,000 population (Qurashi et al., 2023; Vithayathil & Khan, 2022). Although the incidence of CCA is not too high, the mortality rate is very high. CCA has a poor prognosis because most cases are diagnosed at an advanced stage and the availability of limited treatment options (Surya et al., 2023). This can be seen from the 5-year survival rate after therapy of only 7-20% (Qurashi et al., 2023). Characterization of individual CCA patients at the genomic, epigenetic, and molecular levels is an indispensable approach to determine its pathogenesis due to the high heterogeneity of CCA. Therefore, CCA needs to be further understood to find new therapies and treatments that are based on the characteristics of each individual's CCA (Banales et al., 2020).

In the pathogenesis of CCA, there are clinically relevant molecular changes that are expressed

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differently in gallbladder cancer, intrahepatic CCA, and extrahepatic CCA. Based on the NCCN Guidelines for CCA in 2023, there is a recommendation for targeted therapy as further treatment in patients with unresectable or metastatic CCA indicated based on a comprehensive molecular profile (Benson et al., 2023).

Method

In this writing, a literature study method is used by collecting several relevant literatures from various references. The topics raised focus on cholangiocarcinoma and guideline updates. Literature searches were conducted using the Google Scholar search engine and the National Center of Biotechnology Information (NCBI) with search keywords, namely "Cholangiocarcinoma", "management cholangiocarcinoma", "guideline cholangiocarcinoma". The database was taken from references published in ScienceDirect, Researchgate, National Comprehensive Cancer Network, and PubMed published in the last 10 years. From various databases, the literature used and according to the selection criteria amounted to 50 articles.

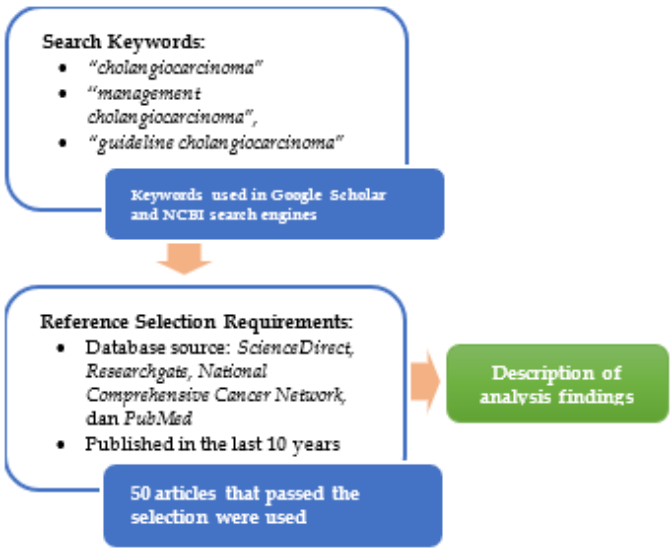

Figure 1. The research flow chart

Result and Discussion

Epidemiology

CCA is a rarer cancer than other cancers and only accounts for 3%-5% of all gastrointestinal cancers (Qurashi et al., 2023; Turati et al., 2022). Geographically, the incidence and mortality of CCA vary greatly. This is thought to be due to differences in geographic risk factors and genetic determinants (Khan et al., 2019). CCA usually occurs between the ages of 60 and 70 years with perihilar CCA being the most common CCA. In addition, CCA cases are more common in men than women (Qurashi et al., 2023). The highest incidence of CCA occurs in Asia, such as northeastern Thailand (85 cases per 100,000 population) as the highest global case followed by Northern and Central Thailand (14.5 cases per 100,000 population) and Gwangju in South Korea (8.8 cases per 100,000 population) (Khan et al., 2019; Qurashi et al., 2023; Turati et al., 2022). Intrahepatic CCA has experienced increasing mortality over the past decade in most regions. In European countries, Ireland and the UK have the highest mortality rates with values above 2 cases per 100,000 population. For the North American region, Canada is the country with the highest intrahepatic CAA mortality with a rate of 1.82 cases per 100,000 population. Then, the East Asian region also experienced an increase in mortality in intrahepatic CCA, such as Korea and Singapore showing mortality rates above 2.5 per 100,000 population (Qurashi et al., 2023; Vithayathil & Khan, 2022).

In the case of extrahepatic CAA, East Asia is the region with the highest mortality. This can be seen in Japan and South Korea which have mortality rates above 2 cases per 100,000 population (Vithayathil & Khan, 2022). In Europe, only Hungary and Germany have mortality rates above 1 case per 100,000 population compared to other European countries (Qurashi et al., 2023). From these statistics, the mortality rate in intrahepatic CAA tends to be higher than extrahepatic CAA (Labib et al., 2019).

The majority of CCAs are diagnosed at an advanced stage, resulting in poor prognosis with a 5-year survival rate of only 7-20% (Qurashi et al., 2023).

Etiology

Histologically, most perihilar and distal CCAs are mucinous adenocarcinomas or papillary tumors. Then, intrahepatic CCA histologically shows two variations, namely small intrahepatic CCA originating from small intrahepatic ducts, progenitor cells, and mature hepatocytes with acinar adenocarcinoma morphology with nodules and invasive to liver parenchymal tissue without mucin production and large intrahepatic CCA originating from large intrahepatic ducts or peribiliary glands based on columnar tumor cells resembling mucinous adenocarcinoma (Kendall et al., 2019; Testa et al., 2023). Currently, CCA cases cannot be explained by identifiable risk factors so that there is a suspicion of the involvement of genetic components in the pathogenesis of CCA (Clements et al., 2020). There is significant variation in risk factors in different regions. Of the identifiable risk factors, the high incidence of CCA in Southeast Asia is due to infection with the Opisthorchis viverrine parasite (Geramizadeh, 2020; Testa et al., 2023; Turati et al., 2022). Then, in general, common bile duct

cysts have a strong relationship to CCA, both intrahepatic CCA and extrahepatic CCA (Clements et al., 2020).

Pathogenesis

CCA develops starting from dysplastic and in-situ lesions with a complex process of carcinogenesis. There are two precursor lesions that affect molecular cholangiocarcinogenesis, namely Biliary epithelial neoplasia (BilIN) and intraductal papillary neoplasms of the bile duct (IPNB) (Geramizadeh, 2020; Kendall et al., 2019). BilIN is stated as an in-situ malignancy with micropapillary dysplasia in the bile duct which is grouped into three categories (BilIN 1-3) based on the degree, area of intraepithelial cells, and nuclear atypia. Then, IPNB is a biliary manifestation of classic intestinal adenocarcinoma. These lesions can be multiple and located inside or outside the hepatic duct (Kendall et al., 2019). In the cell cycle and proliferation, BilIN and IPNB involve the molecules P21, P53, and cyclin D1. However, there are differences in the mucin profile of the two lesions.

BilIN overexpresses MUC-1 while IPNB does not (Geramizadeh, 2020). Chronic inflammation can explain the molecular pathogenesis pathway of CCA that affects a series of intracellular pathways in the carcinogenesis process (Labib et al., 2019). The presence of inflammatory mediators in large amounts, such as the cytokines Interleukin-6 (IL-6) and Tumor Necrosis Factor α (TNF-α), causes progressive mutations in tumor suppressor genes and DNA mismatch-repair, resulting in cell proliferation. The P21 molecule (a mediator that inhibits cell division) decreases due to the presence of IL-6 which activates p38 MPAK for differentiation and proliferation so that cells undergo mitosis. In addition, the presence of an increase in the enzyme Activation-Induced Cytidine Deaminase (AID) due to the cytokine TNF-α causes DNA mutations by converting cytosine to uracil. This causes various somatic gene mutations, such as the tumor suppressor gene P53 (Labib et al., 2019).

Clinical Manifestations

CCA in the early stages usually does not show any symptoms (Banales et al., 2020). Jaundice is a common symptom in CCA patients when there is bile duct obstruction (Forner et al., 2019). Then, there are several other accompanying symptoms experienced by CCA patients, namely abdominal pain, acholia pruritus, malaise, night sweats, athenia, nausea, weight loss (Banales et al., 2020).

Risk Factors

Risk Factors for All Types of CCA Choledocal Duct Cysts

In a meta-analysis, choledocal duct cysts were strongly associated with intrahepatic and extrahepatic CCA (Clements et al., 2020). Choledochal duct cysts are congenital disorders characterized by dilatation of the intrahepatic and extrahepatic bile ducts (Gyawali et al., 2021). This disorder causes obstruction of bile flow, reflux of pancreatic enzymes, and increased bile acid concentrations that may contribute to malignant transformation of the epithelium in the cystic wall of the bile duct (Khan et al., 2019).

Risk Factors for Intrahepatic CCA Cirrhosis

Cirrhosis is known to be a high risk for CCA, especially in intrahepatic CCA (Clements et al., 2020; Khan et al., 2019). Cirrhosis is a form of further liver damage. The liver organ experiences decreased function due to changes in the structure of the liver parenchyma by fibrosis and generative nodules. The increased risk of intrahepatic CCA due to cirrhosis is associated with the process of increased cell proliferation, release of inflammatory cytokines, and liver fibrosis (Khan et al., 2019).

Hepatitis

Hepatitis B virus (HBV) and C virus (HCV) infection are risk factors in the development of CCA, especially in the intrahepatic type of CCA (Khan et al., 2019). Hepatitis viruses have an effect on the intrahepatic bile ducts (Clements et al., 2020). This increased risk occurs due to the carcinogenic effects of the hepatitis virus on target cells. In addition, viral infections can cause chronic liver inflammation, thereby stimulating cell proliferation which increases the risk of malignant cell transformation (Khan et al., 2019; Navas et al., 2019).

Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a disease consisting of Crohn's disease (CD) and ulcerative colitis (UC) which is characterized by chronic inflammation of the digestive tract. Chronic inflammation increases the risk of gastrointestinal malignancy (Yadlapati, 2021). In a meta-analysis study, IBD has a risk of CCA, especially in intrahepatic CCA. Then, for the type of ulcerative colitis and Crohn's disease, it was proven to be associated with the risk of CCA. This risk is associated with chronic inflammation and microbiome dysbiosis caused by both types of IBD (Khan et al., 2019).

T2DM

Type 2 diabetes mellitus is associated with the risk of CCA, especially in intrahepatic CCA (Khan et al., 2019). T2DM is considered an independent risk factor for cholelithiasis which is one of the main risk factors for CCA. Inflammatory cytokines produced by adipose tissue, such as interleukin-6, monocyte chemoattractant protein, and plasminogen activator inhibitor-1, may play an important role in carcinogenesis, cancer

progression, and poor prognosis. This may be a possible mechanism by which diabetes causes CCA (J. Li et al., 2015). Compensatory hyperinsulinemia in diabetes has been shown to stimulate cancer cell growth. However, the relationship between diabetes and CCA due to other intermediary factors, such as obesity and non-fatty liver disease, is still unclear (Khan et al., 2019).

Risk Factors for Extrahepatic CCA
Choledocholithiasis & Cholelithiasis

Choledocholithiasis and cholelithiasis confer a higher risk of extrahepatic CCA (Khan et al., 2019). The increased risk increases with gallstone size, epithelial calcification, and disease duration. However, the relationship between intrahepatic CCA and choledocholithiasis and cholelithiasis is not yet clearly understood. Choledocholithiasis descending from the intrahepatic bile duct can cause chronic inflammation of the intrahepatic bile duct epithelium which is related to the pathogenesis of CCA (Cai et al., 2015).

Smoking

Smoking has been shown to have a tumorigenic effect on various malignancies, including the oral cavity, pharynx, larynx, lung, esophagus, stomach, pancreas, liver, cervix, and kidney (Huang et al., 2017). In a study, smoking habits were said to have a higher risk of extrahepatic CCA. Compounds in tobacco have carcinogenic effects on biliary epithelial cells (Khan et al., 2019). However, the causal relationship between smoking in determining the risk of CCA is still unclear and is likely to be a common risk factor for malignancy (Clements et al., 2020; Khan et al., 2019).

Diagnosis
Radiography Examination
MRCP

Magnetic resonance cholangiopancreatography (MRCP) is the recommended radiographic modality in diagnosing CCA because of its proven sensitivity, specificity, and accuracy (Benson et al., 2023; Lee et al., 2017). MRCP has the ability to assess the bile ducts, blood vessel anatomy, and microvascular infiltration, thus helping in evaluating patient prognosis (Forner et al., 2019; Vogel et al., 2022). In addition, MRCP can differentiate between hepatocellular carcinoma (HCC) and CCA. MRCP with gadoxetic acid contrast in mixed HCC-CCA will obtain a picture of strong and irregular edge enhancement while CCA shows a lobe shape, target appearance, and weak edge enhancement (Forner et al., 2019; Shin et al., 2023). However, MRCP still has contraindications in the form of patients under 10 years of age (Patel et al., 2022).

PET

Positron emission tomography fluorodeoxyglucose (FDG-PET) is generally used in the evaluation of CCA staging (Banales et al., 2020; Krishna et al., 2022; Shin et al., 2023). PET has the best ability in monitoring regional lymph node metastases or distant metastases (Forner et al., 2019; Shin et al., 2023; Vogel et al., 2022). CCA can be detected on FDG-PET because the bile duct epithelium absorbs high glucose. In addition, CCA is a tumor that is avid to fluorodeoxyglucose (Shin et al., 2023).

PET or combined PET/CT can detect nodular CCA as small as one centimeter, but is less effective against infiltrative tumors that may not absorb FDG (Krishna et al., 2022). Malignant and benign lesions are distinguished by semiquantitative assessment based on the degree of uptake and the ratio of tumor to normal liver. However, the current cutoff value for differentiating lesions has not been determined (Shin et al., 2023). Furthermore, FDG-PET can still produce false positives in biliary inflammation or false negatives in cases of mucinous tumors (Forner et al., 2019).

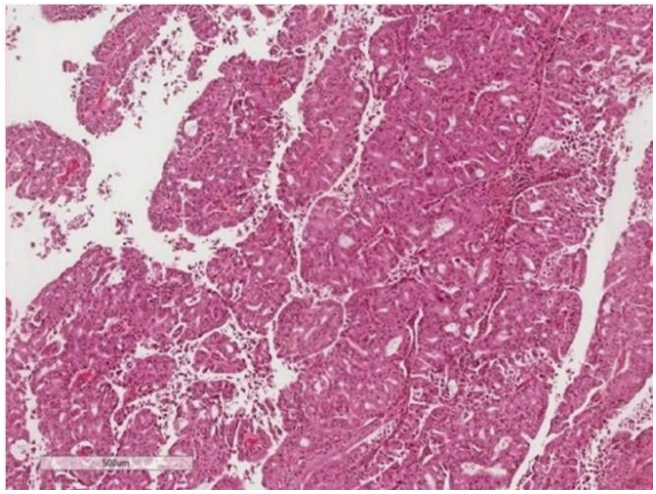

Figure 2. Histopathological picture of CCA HES x100 staining (Guedj, 2022)

Histological Examination

A biopsy should be performed to confirm the diagnosis of CCA. This step requires adequate imaging to guide biopsy sampling (Forner et al., 2019). Endoscopic retrograde cholangiopancreatography (ERCP) can be a guiding modality in biopsy sampling and treatment and assessment of bile duct obstruction (Vogel et al., 2022). In addition, there are other modalities, namely endoscopic ultrasound (EUS) combined with a fine needle or brushing method. EUS can obtain samples from tumor tissue and enlarged lymph nodes. Fine needle EUS is more sensitive than brush ERCP in diagnosing extrahepatic CCA. The fine needle in EUS minimizes contamination of the bile duct that may occur during ERCP. However, fine needle EUS

has lower sensitivity in diagnosing intrahepatic CCA (Shin et al., 2023).

Hepatobiliary Tests

Liver and bile duct function tests are the initial examinations performed on patients suspected of CCA (Benson et al., 2023; Vogel et al., 2022). The examination aims to determine the occurrence of conditions such as inflammation, liver or bile duct damage, HBV and HCV infections, and IBD (Vogel et al., 2022). Examination of bilirubin, gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), and serum transaminases AST and ALT are performed to identify the presence of cholestasis in patients suspected of CCA (Shin et al., 2023). In a study observed a statistically significant difference in age between groups, as well as an indication of a worse prognosis for hepatocholangiocarcinoma (HCCA).

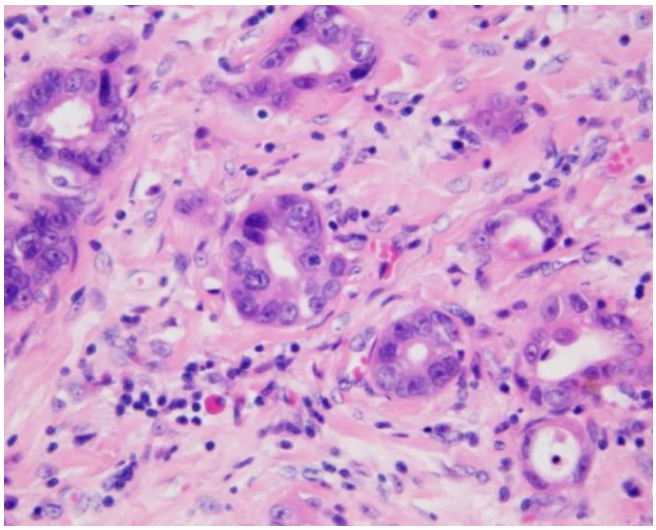

Figure 3. Moderately differentiated ICC characterized by irregular infiltrative glands lined by columnar and slightly pleomorphic cells with HES ×40 eosinophilic cytoplasm (Vijgen et al., 2017).

Patients with HCCA had significantly higher serum ALT and BILT levels. These elevated serum BILT and ALT levels are consistent with previous studies and may be due to the release of enzymes from tumor cells, tumor infiltration and growth along the bile duct wall, wider and/or more severe stenosis, and more severe liver function impairment. However, these findings are not very useful for predicting malignancy (Pang et al., 2021). In patients with extrahepatic CCA, there is an increase in total bilirubin, direct bilirubin, ALP, and GGT. In the early stage, AST and ALP can be in the normal range, but hepatocyte cell damage due to persistent cholestasis can increase transaminase levels. Intrahepatic CCA patients usually have abnormal ALP levels, but serum bilirubin levels can be normal or increased (Shin et al., 2023).

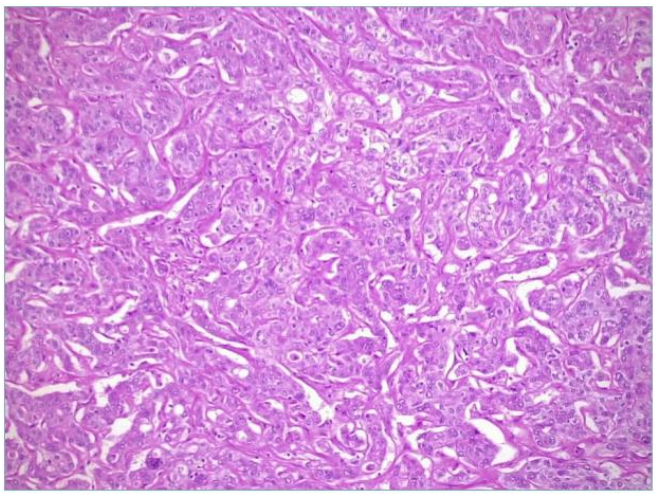

Figure 4. Small duct intrahepatic cholangiocarcinoma consists of cuboidal cells arranged in small tubular or acini structures, with areas of solid growth pattern, and without mucin production (Sarcognato et al., 2021).

Biomarker Test

Carbohydrate antigen (CA 19-9)

The CA 19-9 biomarker is a blood biomarker that can help diagnose CCA with a sensitivity of 50 to 90 percent and a specificity of 54-98 percent. Increased CA-19-9 levels indicate a poor prognosis and an increase in concentrations above 1000 units/mL indicates inoperable disease. In addition, the CA 19-9 biomarker can be used to identify CCA in patients with primary sclerosing cholangitis (Shin et al., 2023).

However, the CA 19-9 biomarker still has some problems in helping diagnose CCA. CA 19-9 may increase in jaundice. Then, specificity is limited because levels can increase in cholangitis or bile duct stenosis. In addition, the CA 19-9 threshold used still varies in distinguishing malignant or benign biliary disease depending on the presence of cholangitis or cholestasis (Shin et al., 2023). Elevated CA 19-9 performs better as a biomarker of aggressive carcinoma and a predictor of poor clinical outcomes by reducing the effect of bile duct obstruction in patients with distal CCA (Jiang et al., 2021).

CEA

CEA, a potent tumor marker in many gastrointestinal malignancies, has also attracted attention as a potential tumor marker in hepatobiliary malignancies. In one study, CEA was more accurate in predicting long-term survival after cholangiocarcinoma resection than CA 19-9 (Jaklitsch & Petrowsky, 2019). High CEA expression was significantly associated with tumor size (Qiang et al., 2021).

Carcinoembryonic antigen (CEA) levels may be elevated in CCA. However, this biomarker is not specific for CCA and may be associated with other tumors or malignancies (Shin et al., 2023). Blood CEA levels greater

than 5.02 ng/mL showed a sensitivity of 68% and a specificity of 82% in the diagnosis of CCA. CEA can be used to monitor treatment effects and identify recurrence when CA19-9 levels do not increase (Shin et al., 2023).

AFP

Alpha-fetoprotein (AFP) testing can be considered in patients with suspected CCA because the diagnosis of HCC and intrahepatic CCA is difficult to distinguish (Benson et al., 2023). In general, serum AFP is used in the diagnosis of HCC and germ cell tumors. AFP has high specificity for identifying HCC but low sensitivity and specificity for CCA (Shin et al., 2023).

Interestingly, about 22.1–35.8% of patients with intrahepatic CCA also have high AFP levels, making patients misdiagnosed as hepatocellular carcinoma (HHC) before surgery. Therefore, it is not uncommon for patients with ICC to have high AFP levels, and physicians should interpret this test value with caution, because the prognosis of HCC is very different from ICC. However, there are few reports of AFP elevation in patients with ICC, and the long-term outcomes of these patients are largely unknown due to the large sample size (Zhang et al., 2021).

Treatment Management

The initial action in the management of CCA patients is an initial examination to assess resectability in intrahepatic and extrahepatic CCA. The assessment includes the level of bile duct obstruction, liver invasion, vascularization, lymph nodes, and the presence of metastases (Vogel et al., 2022). Multidisciplinary review in imaging analysis involves radiologists and surgeons to assess the stage of cancer and determine treatment options (Benson et al., 2023).

Based on the 2023 NCCN Guidelines for Biliary Tract Cancer, CCA management consists of (Benson et al., 2023):

Surgery

Complete surgery with negative margins is the only potentially curative treatment for patients with operable disease. Pre-surgical exploration should be performed with the scope of assessing multifocal liver disease, lymph node metastases, and distant metastases as they are contraindications for surgery. Porta hepatis lymphadenectomy can provide information on metastases which are prognostic indicators of survival. Therefore, regional porta hepatis lymphadenectomy is recommended (Benson et al., 2023).

The type of surgical procedure performed is based on the anatomical location of the tumor in the bile duct. In mid-biliary duct tumors that do not involve the liver or pancreas, bile duct excision with frozen section assessment of the proximal and distal bile duct edges and pancreaticoduodenectomy can be performed. In rare cases such as extensive bile duct tumors, combined pancreaticoduodencectomy and liver resection need to be performed. However, this operation is associated with high morbidity and unclear survival. In patients with hilar CCA, extended liver resection with caudate lobectomy is recommended because it touches or invades the middle liver (Cillo et al., 2019). Pancreaticoduodenectomy can also be performed in patients over 75 years of age. In a study, age factors showed no significant difference in outcomes after the procedure (Paiella et al., 2017). Furthermore, liver resection is contraindicated in patients with small liver volume and chronic liver disease (Barros et al., 2022)

Locoregional Therapy

In several small retrospective studies of patients with unresectable or metastatic intrahepatic CCA without extrahepatic disease, locoregional therapy has been shown to be safe and effective. These therapies can include radiofrequency ablation, transarterial chemoembolization (TACE), TACE with a combination of drug-eluting beads (DEB-TACE), radioembolization (TARE) with a combination of Y-90 microspheres, and radiotherapy (Benson et al., 2023).

TACE treatment has the disadvantage of causing ischemia and hypoxia in embolized tissue, which triggers the production of proangiogenic factors such as VEGF, which further enhances tumor angiogenesis. Therefore, the use of combination therapy of TACE and apatinib can improve the efficacy of advanced intrahepatic CCA treatment (Zhang et al., 2023).

Adjuvant Chemotherapy and Chemoradiation

The main limitation in achieving cure for patients with biliary tract cancer is recurrence after surgery. This is a consideration for the use of adjuvant therapy which can be given for six months. In a systematic review, patients who underwent surgery and adjuvant therapy had a higher survival than surgery alone. Chemotherapy or chemoradiation therapy was associated with better benefits than radiotherapy alone. The greatest benefit of this therapy was in patients with positive lymph node disease and macroscopic residual disease (Benson et al., 2023).

In a retrospective study of resected extrahepatic CCA patients, adjuvant chemoradiation improved local control and survival. However, distant metastasis was the most common factor for treatment failure. Adjuvant chemoradiation may have significant survival benefits in patients with T3 or T4 tumors or patients at risk of locoregional recurrence. Concomitant chemoradiation with gemcitabine is not recommended due to the toxicity associated with this treatment (Benson et al., 2023).

Gemcitabine monotherapy or a combination of cisplatin and capecitabine are the recommended chemotherapy regimens. Then, patients with extrahepatic CCA with positive margins after resection or local gross residual and intrahepatic CCA with local residual can use fluoropyrimidine-based chemotherapy or gemcitabine followed by fluoropyrimidine-based chemoradiation or vice versa. Guidelines for the use of adjuvant chemotherapy are not specific to a particular type of biliary tract cancer due to limited data and heterogeneity of patient populations in published studies (Kelley et al., 2023).

Advanced Stage Treatment

Treatment options for advanced CCA may include systemic therapy, palliative radiotherapy, radiotherapy in combination with a fluoropyrimidine, consideration of locoregional therapy, and best supportive therapy. The choice of next-line systemic therapy in progressive disease depends on several factors, such as prior treatment regimen, somatic molecular testing results, and degree of liver dysfunction (Benson et al., 2023).

Chemotherapy

In the chemotherapy treatment of patients with advanced CCA, gemcitabine-based and fluoropyrimidine-based combinations are recommended. These combinations can be gemcitabine with cisplatin, gemcitabine with oxaliplatin or capecitabine, capecitabine with oxaliplatin, FOLFOX, gemcitabine combined with albumin-bound paclitaxel, gemcitabine combined with cisplatin and bound paclitaxel, and single agents of fluorouracil, capecitabine, and gemcitabine (Benson et al., 2023). The good safety and moderate treatment intensity of transarterial infusion with the FOLFOX regimen mean that it is a perfect choice for the multiagent treatment of intrahepatic CCA, which benefits from a combination of targeted therapy, radiotherapy, and other treatment options (Li et al., 2022). The combination of gemcitabine or leucovorin with fluorouracil was excluded due to ineffectiveness and high toxicity (Vogel et al., 2024). Combination of Immunotherapy and Chemotherapy

The recommendation for first-line systemic treatment for unresectable or metastatic CCA is category one therapy of choice, a combination of durvalumab, gemcitabine, cisplatin, and a combination of pembrolizumab, gemcitabine, cisplatin (Benson et al., 2023). Patients who experience recurrence more than six months after surgery or additional therapy may be recommended a combination of durvalumab, gemcitabine, and cisplatin. This combination is an option for progressive disease in patients who have not previously been treated with checkpoint inhibitors (Benson et al., 2023). Current checkpoint inhibitors target the PD-1 and PD-L1 checkpoints (Jakubowski & Azad, 2020).

However, the use of chemotherapy requires special careful attention. Chemotherapy drugs are thought to only kill cancer cells specifically, but it is now known that chemotherapy drugs also damage normal cells, causing side effects that depend on the dose of chemotherapy such as fatigue, nausea, hair loss, vomiting, and even death can occur in severe cases (Aslam et al., 2014).

Targeted Therapy

Targeted therapy is a therapy that focuses on the molecular characteristics of certain cancer cells so that it can understand the process of cancer cell division and movement in the body. Biliary Tract Cancer is known to contain clinically relevant molecular changes that are differentially expressed in gallbladder cancer and intrahepatic and extrahepatic CCA. Given the emerging evidence regarding actionable molecular targets for treating BTC, comprehensive molecular profiling is recommended for patients with unresectable or metastatic BTC (Benson et al., 2023).

Targeted molecules include NTRK fusion with NTRK inhibitors such as entrectinib and larotrectinib, DNA repair regulatory gene mutations with pembrolizumab, dostarlimad-gxly, ipilimumab and Nivolumab combinations, BRAF gene mutations with dabrafenib and trametinib combination therapy, FGFR2 fusion with furibatinib and pemigatinib drug options, IDH1 gene mutations with ivosidenib, HER2 oversecretion with trastuzumab and pertuzumab combination therapy. FGFR is a family of four transmembrane receptors with intracellular tyrosine kinase domains. When FGFR receptors are activated, the Ras/RAF/MEK, JAK/STAT, and PI3K/Akt pathways are then activated. Disruption of FGF signaling is associated with proliferation, malignant cell migration, and angiogenesis in a large number of tumors (Proskuriakova & Khedr, 2022).

IDH inhibitors have been shown to inhibit the growth of tumor cells harboring specific IDH mutations. AG-120/ivosidenib is a potent first-in-class oral mutant IDH1 inhibitor that is being investigated in a Phase I study in intrahepatic CCA (Kelley et al., 2020). As recently studied in patients with intrahepatic cholangiocarcinoma, pemigatinib and other targeted therapies may complement chemotherapy delivered systemically or directly to the liver via hepatic artery infusion (Abou-Alfa et al., 2020).

There are several efforts to reduce the side effects of targeted FGFR inhibitor therapy such as dietary modification of plant-based foods and phosphate-lowering therapy (phosphate binders and phosphate agents) can reduce hyperphosphatemia. Then,

optimization of nutrition and sleep is needed to eliminate fatigue, fluid intake and probiotic supplements can improve diarrhea symptoms (Du et al., 2023).

Prognosis

In recent years, several advances have been made in therapeutic approaches. However, CCA patients usually present with advanced disease and are associated with poor prognosis (Benson et al., 2023). The prognosis of patients has not improved in the last decade, with a 5-year survival of only 7-20% and a disappointing tumor recurrence rate after resection (Elvevi et al., 2022). Currently, proteins and cytokines are considered as potential biomarkers in diagnostics and prognostics. Several biomarkers such as Cytokeratin-19 fragment (CYFRA 21-1), MMP-7, osteopontin, periostin, IL-6, CYFRA 21-1, osteopontin, CA19-9, can be negative prognostic factors in CCA and are associated with disease progression. In addition, there is a positive prognostic factor in the form of the biomarker p27 whose high expression levels are associated with increased survival (Banales et al., 2020). There is also a new biomarker, namely Acyl-CoA synthetase long-chain family member 4 ACSL4, which is consistently high in CCA patients with poor prognosis (Liu et al., 2023). Then, there is research that circulating tumor cells have the potential to predict the survival and characteristics of CCA patients (Banales et al., 2020; Giovannoni & Villanueva, 2016; Rodrigues et al., 2021). CCA usually experiences metastasis to the lymph nodes, peritoneum, liver, and sometimes can reach the brain (Ioffe et al., 2021).

Conclusion

Cholangiocarcinoma (CCA) is a malignancy caused by abnormal DNA mutations that result in uncontrolled cell growth. Clinical manifestations of CCA do not show any symptoms in the early stages. Jaundice is the most common symptom in the advanced stages. The prognosis of CCA remains poor even after therapy. The 5-year survival rate is only 20% after therapy and the recurrence rate is still disappointing after resection. CCA has a poor prognosis because most cases are diagnosed at an advanced stage and the availability of treatment options is limited. Diagnostic steps are carried out using radiographic modalities and laboratory tests confirmed by histological examination. Management based on the 2023 NCCN Guidelines for Biliary Tract Cancer includes determining the staging of cancer, surgery, locoregional therapy, chemotherapy, chemoradiation, and targeted therapy which are additional options for patients today.

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No conflict of interest.

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