National Guidelines for the Diagnosis and Treatment of Hilar Cholangiocarcinoma

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Abstract: A consensus meeting of national experts from all major national hepatobiliary centers in the country was held on May 26, 2023, at the Pakistan Kidney and Liver Institute & Research Center (PKLI & RC). The Pakistan Society of Study of Liver Diseases (PSSLD) and PKLI & RC jointly organized this meeting. This effort was based on a comprehensive literature review to establish national practice guidelines for hilar cholangiocarcinoma (hCCA). The consensus was that hCCA is a complex disease and requires a multidisciplinary team approach to best manage these patients. This coordinated effort can minimize delays, give patients a chance for curative treatment and effective palliation. The International Classification of Diseases (ICD 2022) code system was used to define the nomenclature of cholangiocarcinoma. Obstructive jaundice is the leading clinical symptom of hilar cholangiocarcinoma. The diagnostic & staging work up includes high quality CT, MRI, and MRCP. The endoscopic retrograde cholangiography (ERCP) with brush cytology or biopsy is key for diagnosis, however histopathologic confirmation is not always required before resection. Endoscopic ultrasound with FNA of regional lymph nodes and PET scan are useful adjuncts for staging. The only curative treatment is the surgical resection of the biliary tree and involved hemi liver based on the Bismuth-Charlotte classification. Selected patients with unresectable hilar cholangiocarcinoma can be considered for liver transplantation. Adjuvant chemotherapy should be offered to patients with high risk of recurrence. The use of preoperative biliary drainage and the need for portal vein embolization (PVE) should be based on the local multidisciplinary discussions. Patients with acute cholangitis can be drained with endoscopic or percutaneous biliary drainage. Palliative chemotherapy with cisplatin and gemcitabine has shown improved survival in patients with irresectable and recurrent hilar cholangiocarcinoma.

Development of guidelines: With no national registry and lack of formal hepatobiliary (HPB) centers; diagnosis of hCCA remained bad news for unfortunate patients for three decades in Pakistan. However, more recently, with the development of HPB centers in most of the major cities, patients with hCCA have a silver lining for curative treatment. There is currently no national consensus for the appropriate diagnosis and treatment of hCCA. The need for such national guidelines was realized and with the collaborative efforts of PSSLD and PKLI & RC, a meeting of national experts from all major HPB centers was arranged on May 26, 2023, at PKLI & RC, Lahore, Pakistan.

Intent: These guidelines are developed to standardize the diagnostic approach and treatment strategy of patients across the country. The basis of guidelines is the literature review of randomized controlled trials, meta-analyses, case cohort, prospective, and retrospective studies. These guidelines should not be regarded as the standard of care for all patients. Patients must be managed based on all available clinical data for that case. The guidelines are subject to change, considering future advances in scientific knowledge.

Level of evidence: The scientific evidence used as the basis of these guidelines is graded according to the quality of evidence using the Oxford Centre for Evidence based Medicine level of evidence. (Table 1).
Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine (adapted from The Oxford 2011 Levels of Evidence).

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
<th>Simple model for high, intermediate, and low evidence</th>
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<tbody>
<tr>
<td>1</td>
<td>Systematic reviews (SR) (with homogeneity) of randomized controlled trials (RCT)</td>
<td>Further research is unlikely to change our confidence in the estimate of benefit and risk</td>
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<tr>
<td>2</td>
<td>Randomized controlled trials (RCT) or observational studies with dramatic effects; systematic reviews (SR) of lower quality studies (i.e., non-randomized, retrospective)</td>
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<tr>
<td>3</td>
<td>Non-randomized controlled cohort/follow-up study/control arm of randomized trial (systematic review is generally better than an individual study)</td>
<td>Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate</td>
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<tr>
<td>4</td>
<td>Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)</td>
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<tr>
<td>5</td>
<td>Expert opinion (mechanism-based reasoning)</td>
<td>Any estimate of effect is uncertain</td>
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Table 2. Grades of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Wording</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Strong</td>
<td>Shall, should, is recommended. Shall not, should not, is not recommended.</td>
<td>Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility</td>
</tr>
<tr>
<td>Weak or open</td>
<td>Can, may, is suggested. May not, is not suggested.</td>
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Epidemiology

Cholangiocarcinoma (CCA) is the second most common liver-related cancer. It accounts for 10-20% of mortalities from hepatobiliary malignancies(1). Anatomically, it is classified as intrahepatic and extrahepatic cholangiocarcinoma. Extrahepatic cholangiocarcinoma (eCCA) is then further classified as hilar/perihilar (hCCA) and distal (dCCA) based on location. Intrahepatic cholangiocarcinoma (iCCA) occurs above the second-order bile ducts, while the insertion of the cystic duct distinguishes hCCA and dCCA types(2)[Figure-1]. Hilar cholangiocarcinoma or Klatskin tumor, is the most common type, accounting for 40-60% of CCA cases, followed by dCCA at 20-30% and iCCA at 10-20%(3). Variances in etiology, risk factors, pathobiology, clinical management, and prognosis are seen based on these anatomical differences. Until 2022, the International Classification of Diseases (ICD) did not have a specific code for CCA, resulting in misclassification and difficulty in identifying disease characteristics. The ICD-11 codes were published on January 1, 2022, and now include separate codes for each subtype of CCA (4) [Fig 1]. These new codes will make it easier to differentiate between the three subtypes of CCA.
Cholangiocarcinoma typically occurs in individuals over the age of 40, most commonly in the seventh decade of life\(^{(5)}\). Men are more likely to develop CCA than women, with a ratio of 1:1.2-1.5\(^{(6)}\). Incidence has been on the rise globally in recent decades, with an increase in mortality more for iCCA\(^{(7)}\). It has a significant geographical variation and is less common in Western countries, compared to some parts of Asia. This difference is mainly attributed to the higher prevalence of established risk factors in some Asian countries. Incidence per 100,000 ranges from 85 in northeast Thailand to 0.4 in Canada\(^{(8)}\).

Epidemiological data on hCCA is lacking from Pakistan and is limited to a handful of small studies. Recently a National Cancer Registry report from Pakistan (2015-2019), showed liver and intrahepatic bile duct cancers represent 4.43% of all cancers, with a higher prevalence in men compared to women (6.73 vs 2.45)\(^{(9)}\). In a retrospective analysis of 245 patients with biliary tract malignancy at Aga Khan University, 11.8% were diagnosed to have CCA\(^{(10)}\). In another report from Lahore, a total of 34 patients were operated on for CCA over 9 years, hCCA represented 53% of these cases\(^{(11)}\). Dar et al. in their analysis of 24 patients with hCCA, reported a median age at presentation of 49 (23-73) years, with male to female ratio of 1.4:1\(^{(12)}\).

![Figure 1: Anatomical Classification of Hilar Cholangiocarcinoma](image-url)
Risk factors

The causes of hCCA remains obscure in many patients. The role of genetic factors remains poorly defined(13,14). The estimated lifetime incidence of CCA with Primary Sclerosing Cholangitis (PSC) ranges up to 20%(15). While PSC is a known risk factor for CCA(16), it is attributed to no more than 10% of cases of CCA(17). Hepatobiliary flukes Opisthorchis viverrini (O. viverrini) and Clonorchis sinensis (C. sinensis) have been linked to the development of CCA in Southeast Asia, regardless of site(18). The strongest risk factors apart from liver fluke and PSC for both iCCA and eCCA were biliary cysts(19), stones, along with cirrhosis, hepatitis B and hepatitis C. In a recent meta-analysis(20), Choledochal cysts conferred the greatest risk of both iCCA and eCCA with pooled ORs of 26.71 (95% CI 15.80–45.16) and 34.94 (24.36–50.12), respectively.

Available cohort and case-control studies indicate that high levels of alcohol consumption and tobacco smoking can also increase the likelihood of developing CCA including hCCA(21). Conditions such as diabetes, obesity, non-alcoholic fatty liver disease, and metabolic syndrome are believed to contribute to the increasing incidence of CAA(3). However, no significant associations were found between hypertension and obesity in a recent systemic review (20). Diabetes has been identified as a significant risk factor for both iCCA and eCCA, with odds ratios of 1.8 (95% CI 1.5-2.1) and 1.5 (95% CI 1.3-1.8), respectively (22) (Table 1).

Association with other risk factors like IgG4-associated sclerosing cholangitis (23,24), abnormal junction between the bile and pancreatic duct (23), typhoid infection (25,26) and infection with Helicobacter bilis (27,28) need more research before a definitive conclusion can be made.

<table>
<thead>
<tr>
<th>Established</th>
<th>Less established</th>
<th>Potential (Inconclusive data)</th>
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<tbody>
<tr>
<td>Primary sclerosing cholangitis (PSC)</td>
<td>Inflammatory bowel disease</td>
<td>Obesity</td>
</tr>
<tr>
<td>Choledochal cysts</td>
<td>Cirrhosis</td>
<td>Tobacco smoking</td>
</tr>
<tr>
<td>Parasitic infections</td>
<td>Hepatitis B and C viruses</td>
<td>Genetic polymorphisms</td>
</tr>
<tr>
<td>Hepatolithiasis and</td>
<td>Diabetes</td>
<td></td>
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<tr>
<td>Choledocholithiasis</td>
<td>Heavy alcohol use</td>
<td></td>
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<tr>
<td>Toxins (Thorotrast contrast agent)</td>
<td>IgG4 related cholangitis</td>
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<td></td>
<td>Abnormal junction between the common bile duct and pancreatic duct</td>
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<tr>
<td></td>
<td>Helicobacter bilis</td>
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<tr>
<td></td>
<td>Chronic typhoid infection</td>
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Table 1: Risk factors for Hilar Cholangiocarcinoma

Recommendations

- Choledochal cyst, primary sclerosing cholangitis, parasitic infestations, hepatolithiasis and choledocholithiasis should be considered as well established risk factors for hCCA (LoE 2; strong recommendation).
- Diabetes, alcohol, smoking, and obesity should be considered as less well established risk factors for hCCA (LoE 3; strong recommendation).
Histo-Morphological Classification
The CCA can be classified based on a). anatomy b). morphology c). histopathology. Anatomical classification has been discussed earlier in section 1.

Morphological:
Initially classified as nodular, massive, and diffuse. Rosai called them as polypoidal and Sclerosing (29). However, at present, the classification from the Japanese group is being followed (29) as below:

1-Mass forming is defined as a small nodule 1-2 cm with bile duct dilatation.
2-Intraductal (polypoidal, sessile or superficially spreading) is along the mucosa. It is confined to mucosa and doesn’t infiltrate deeply till an advanced stage.
3-Periductal is characterized by annular thickening without mass formation and manifests as complete luminal obstruction.

Histological:
Histologically, most are classified as well to moderately differentiated biliary type adenocarcinomas. These are characterized by tubules and glands in a typical desmoplastic stroma with variable inflammatory response. These are further categorized as gastric foveolar, intestinal and biliary types. Sometimes papillary groups and sheets are also seen (30). Perineural and neural invasion is a specific route of invasion, seen in many cases and has prognostic significance. There is also increased invasion of lymphatics(31). A quantitative grading system based on the percentage of gland formation has been proposed in College of American Pathologists (CAP) guidelines and should be followed to standardize reporting(32).

In addition to conventional adenocarcinoma, there are other types i.e., squamous cell carcinoma, adenosquamous carcinoma, mucinous, signet ring cells, neuroendocrine, clear cells and poorly differentiated. Most of these non-conventional carcinomas have a worse prognosis. Two premalignant conditions have also been identified. High grade biliary intraepithelial neoplasm (BillIN) and Intraductal papillary neoplasm of the biliary tract (IPNB)(33)

Immunohistochemistry can help differentiate metastatic disease by identifying the biliary nature of cells. Conventional markers for adenocarcinomas are CK7, CK20, CK19, P53, MUC5AC and MUC1. The markers used for squamous cell carcinoma are CK5/6 and for neuroendocrine carcinoma synaptophysin/chromogranin(34). Lack of mucin production and the expression of HepPar-1, CD10 and glypican-3 helps distinguish hepatocellular carcinoma (HCC) from CCA.

Immunohistochemistry is useful in the following two scenarios; firstly, to differentiate metastatic disease from primary CCA and second to distinguish CCA from Hepatocellular Cancer(35).

Biliary Cytology:
The biliary cytology is reported under six categories; i-unsatisfactory, ii-negative for malignancy, iii-atypical; iv-benign neoplastic lesions, v-suspicious for malignancy, vi-malignant.

Molecular Pathology:
Gene sequencing to assess molecular alterations is now emerging to differentiate between benign and malignant strictures(36). Singhi et al. evaluated a 28-gene next generation sequencing panel using biliary specimens from ERCP. Next generation gene sequencing
improved pathological evaluation of malignancy, improving sensitivity from 35% to 77% for biliary brushings and 52% to 83% for biliary biopsies(37).

Recommendations

- Hilar cholangiocarcinoma should be classified as conventional adenocarcinomas or other unconventional tumors based on biliary cytology or biopsy (LoE 2; strong recommendation).
- College of American Pathologists guidelines should be followed to standardize reporting (LoE 3; strong recommendation).
- Immunohistochemistry may be done in selected cases to aid in diagnosis (LoE 3; weak recommendation).

Laboratory Evaluation

Patients generally present with painless jaundice. The ALT/AST may be normal or minimally elevated. Alkaline phosphatase levels usually rise in conjunction with bilirubin levels. Biochemical tests of liver function (i.e., albumin, prothrombin time [PT]) are normal early in the course of disease. The PT/INR can become elevated with prolonged obstruction, because of vitamin K malabsorption.

None of the tumor markers are highly sensitive or specific for diagnosis. Carbohydrate Antigen 19-9 (CA 19-9) is the commonly used tumor marker. The CA19-9 is mainly synthesized by the pancreatic and biliary ductal cells and can be falsely raised in biliary and pancreatic ductal obstruction from benign diseases (38). Notably, 10% of the patients are non-producers and may have normal CA19-9 levels (39). The CA19-9 can also be produced by epithelial cells in the stomach, colon, uterus, and salivary glands. Elevated levels can also be seen in urological, pulmonary, and gynecological conditions (40).

In patients with PSC, a cut-off value of 129 U/mL had a sensitivity (78.6%), specificity (98.5%), PPV (56.6%) and NPV (99.4%) in predicting CCA (41). Another study reported a cut-off value of 100 U/mL having a sensitivity (53.0%) and NPV (92%) in predicting CCA (39). In a metanalysis published in 2015, the overall pooled sensitivity was 0.72 (0.70–0.75) and specificity was 0.84 (0.82–0.85) (42). The utilization of other tumor markers i.e., CEA and CA-125 in the diagnosis of hCCA is limited due to their low specificity and cannot be interpreted in the setting of obstruction.

The Ig-G4 sclerosing cholangitis (IgG4-SC) commonly affecting elderly men can pose a challenge to the diagnosis of hCCA with several reports in the literature (43–46). With greater recognition of this entity, several guidelines (47–49) now recommend testing for IgG-4 disease in those with suspected hCCA.

Recommendations

- CA 19-9 is a widely used serum tumor marker for suspected hCCA but does not exhibit high sensitivity and should be carefully interpreted as part of the clinical evaluation (LoE 2; strong recommendation).
- Testing for IgG4 cholangiopathy should be obtained in suspected cases of hCCA (LoE 4; strong recommendation).
**Imaging workup**

Ultrasound (US) is generally the first imaging modality for evaluation of obstructive jaundice. It cannot directly diagnose hCCA but may raise suspicion. Once the diagnosis of hCCA is suspected the initial radiological examination is often a cross sectional imaging study, such as multiphasic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) (50,51).

The CT is easily available, quick to perform and does not require breath holding, but carriers a risk of radiation exposure and contrast induced nephropathy. The MRI with MRCP on the other hand has no radiation risk, however, is a longer procedure, needs patient cooperation and may be contraindicated in those with pacemaker and metal implants. While MRI with MRCP is better for soft tissue characterization and may provide an accurate assessment of longitudinal extension in hCCA, it may overestimate vascular invasion, especially after stenting. The CT on the other hand provides better information on vascular invasion (50).

There is no head-to-head comparison of MDCT vs MRI/MRCP in the diagnosis of hCCA. In a systematic review article by Hongchen Zhang et al., CT was the most commonly used modality (52). However, MRI with MRCP is becoming the preferred modality for diagnosis of hCCA in the literature (53) In the Pakistani setting, given limitations of availability, cost and difficulty in acquisition of good quality images, CT scan can be used as the preferred diagnostic modality (54).

Endoscopic Retrograde Cholangiopancreatography and transhepatic cholangiography now have a limited role in the diagnosis and staging of hCCA. These modalities have therefore been abandoned as an initial diagnostic tool. However, they can be used as next step in the evaluation, especially to aide in tissue sampling if needed (55). Over the years there has been shift from invasive diagnostic modalities to non-invasive imaging with increase in their yield (56,57).

PET-CT has no clear diagnostic role in helping evaluate issues of local resectability. However, it appears to add some benefit in detecting distant metastatic disease. According to one study the sensitivity and specificity of PET-CT for detection of distant metastases was 100% each. However, the sensitivity of regional lymph node metastases was 12% (specificity of 96%) (58). In another study PET-CT revealed higher accuracy than CT and MRI in the diagnosis of regional lymph nodes metastases (75.9% versus 60.9%, \( p = 0.004 \)) and distant metastases (88.3% versus 78.7%, \( p = 0.004 \)) (59). More studies on the application of PET-CT are needed to determine its utility in staging (52). Endoscopic ultrasound (EUS with or without FNAC/FNB) may offer another alternate in staging of metastatic lymph nodes (60).

The necessity of establishing a tissue diagnosis prior to surgery depends upon the clinical situation (61). It is not critical for planning surgery in patients with characteristic findings of mass forming malignant biliary obstruction and may not be necessary for planning palliative therapy. Furthermore, tissue sampling with a percutaneous approach with US or CT guidance is not recommended without a visible mass. The ERCP and EUS guided brush biopsies / FNAC have poor sensitivity. Detailed knowledge of mimicking diseases and interpretation of biochemical and imaging modalities may lead to a correct diagnosis without the need for biopsy (62).

Given the complexity in diagnosis and staging, each case of suspected hCCA should be discussed in a Multidisciplinary Team (MDT) meeting. The MDT should comprise of radiologists, advanced GI endoscopists, hepatobiliary surgeons and oncologists to decide the need for further testing.
Role of Endobiliary Procedures in Diagnostic Evaluation
The main purpose of endobiliary interventions in the diagnostic evaluation of hCCA is to establish histological confirmation and disease staging in the context of Bismuth Corlette Classification to determine resectability and offer preoperative planning. Biliary strictures remain indeterminate without confirmatory histology, posing a diagnostic dilemma to stratify management decisions. Although, in patients with hCCA, preoperative histological confirmation may not be required, around 20% with benign biliary strictures may undergo a major surgery for suspected biliary malignancy(63).

The most commonly used modalities to obtain tissue diagnosis in resectable hCCA are ERCP, PTC and intraductal cholangioscopy. Brush cytology, fluoroscopy and cholangioscopy guided forceps biopsy are used to ascertain tissue diagnosis.

Sensitivity of standard brush cytology in review of 1556 cases has been reported 41.6% ± 3.2% (99% CI) with a negative predictive value of 58.0% ± 3.2% (99% CI)(64). Yoon et al. in a meta-analysis revealed pool diagnostic sensitivity of 56.0% (95% confidence interval (CI) 48.8-63.1%, I2 = 83.0%) with brush cytology alone, 67.0% (95% CI 60.2-73.5%, I2 = 72.5%) with biopsy and 70.7% (95% CI 64.1-76.8%, I2 = 42.7%) with brushing & biopsy(65). Supplementary technique such as fluorescence in situ hybridization (FISH) have been suggested to further improve the diagnostic sensitivity. Nanda et al. reported the diagnostic sensitivity of brush cytology alone, brush cytology with FISH, brush with FISH & biopsy to be 27% vs 77% vs 82% respectively(66).

The number of passes also increases the diagnostic sensitivity of brush cytology. Wang et al. in a RCT showed that the sensitivity of brush cytology was 38%, 47%, and 57% in the 10-times, 20-times, and 30-times groups, respectively (P = 0.001)(67). The stricture length of >1cm has also been reported as a predictive factor of positive diagnostic yield on brush cytology (68).

Single operator digital cholangioscopy has emerged as a preferred modality for evaluating indeterminate hilar strictures after inconclusive endobiliary investigations. A systematic review evaluated outcomes of cholangioscopy directed biopsies involving 539 patients and reported a pooled sensitivity of 72% and specificity of 99%(69). Sun et al. in a meta-analysis studied the performance of single-operator cholangioscopy and revealed the pooled sensitivity and specificity of visual impression (90% & 87%) and spy-bite biopsy (69% & 98%) for the diagnosis of indeterminate biliary strictures(70).

The role of EUS in hCCA is to stage the disease and sampling of hilar mass or locoregional lymph nodes. However, tissue acquisition of hilar mass by EUS carries risk of seeding metastasis and should be decided in MDT settings(71). In a meta-analysis, the pooled

Recommendations

- Initial radiological examination should be a cross sectional imaging study, such as a CT or an MRI & MRCP (LoE 2; strong recommendation).
- Treatment planning should be done in the presence of resectable hCCA with characteristic imaging features, tissue diagnosis is not mandatory for such cases (LoE 4; weak recommendation).
- PET-CT may aid in diagnosing distant metastatic disease and should be considered in surgical planning, where added information may change the treatment outcome (LoE 2; weak recommendation).
diagnostic sensitivity and specificity of EUS FNA for malignant hilar strictures was 76% (95% CI, 66%-85%) and 100% (95% CI, 95%-100%), respectively with low adverse event rates (72).

Lymph node metastasis is a strong predictor of poor survival in hCCA patients. Malikowski et al. reported better regional lymph node detection rates with EUS (89%) than cross-sectional imaging (48%) in patients with hCCA and malignancy was confirmed in 16% of nodes after tissue acquisition via EUS-FNA(73). Another retrospective, multicenter cohort study demonstrated that EUS-FNA detected malignant lymph nodes in 14% of potentially resectable hCCA and avoided surgical exploration (74).

Role of Intraductal ultrasound (IDUS) in the evaluation of indeterminate biliary strictures is evolving. In a study of 234 indeterminate biliary strictures, the detection rate of malignancy by ERCP/IDUS was superior to endoscopic trans-papillary biopsy (91% vs 59%, P < 0.0001), EUS (91% vs 74%, P < 0.0001), and CT (91% vs 73%, P < 0.0001)(75).

Recommendations

- ERCP guided brush cytology and targeted biopsy should be the preferred diagnostic modality to obtain histological confirmation in suspicious or indeterminate biliary strictures (LoE 2; strong recommendation).
- Number of passes should be increased to enhance the diagnostic sensitivity of brush cytology (LoE 2; strong recommendation).
- Intraductal cholangioscopy and tissue sampling should be considered in selective cases that remain a diagnostic challenge (LoE 2; strong recommendation).
- In cases with concern for locoregional metastasis, endoscopic ultrasound should be used for staging and tissue sampling (LoE 4; strong recommendation).

Staging

Various staging systems have been introduced to define tumor resectability and guide therapy. In 1975 Bismuth and Corlette presented the first staging system. Their classification focused primarily on the level and extension of the tumor along the biliary ductal system. This classification correlated to the procedure required for surgical excision and the establishment of biliary continuity(76,77).

To define resectability, the Memorial Sloan Kettering Cancer Center (MSKCC) staging was introduced in 1998 and was revised in 2001. They incorporated the portal vein invasion, the resulting hepatic lobar atrophy and the tumor's location and extension of bile duct involvement(78). This provides a framework for defining resectability. However, it does not evaluate the presence of nodal/distant metastasis or arterial involvement.

Mayo Clinic staging was designed for outcome prediction of hCCA patients, rather than surgical resection. The Mayo Clinic staging considered the tumor size and multifocality, vascular invasion, lymph node, extra-regional metastasis, carbohydrate antigen 19-9 (CA19-9) level and performance status to categorize patients into a four-stage system. This staging system reported survival for unresectable hCCA(79,80).

The American Joint Commission on Cancer (AJCC) Staging System, which includes a tumor–node–metastasis (TNM) system is based on pathological findings and is known as pathological staging. It is used postoperatively and has a better prognostic value for resected patients and guides further therapy. The AJCC 8th edition is currently available(81).
To produce a simple and reproducible staging system for hCCA recently the International Cholangiocarcinoma Working Group proposed a new classification based on some parameters from the previous systems(2). The size of the tumor, the extent of the biliary system involvement, hepatic artery and portal vein involvement, lymph node involvement, distant metastases, and the volume of the remnant liver after resection. This system aims to standardize the reporting of hCCA so that resectability and prognosis can be adequately provided.

These staging systems can be supplemented with each other to define resectability, guide the therapy and predict the prognosis in hCCA patients.

**Recommendations**

- The Bismuth–Corlette classification provides the basis for determining the biliary extent of hCCA and should be used for primary staging and deciding on the surgical technique (LoE 1; strong recommendation).
- The Memorial Sloan Kettering Cancer Center staging evaluates blood vessel invasion, liver atrophy, and should be used for predicting resectability (LoE 3; strong recommendation).
- The American Joint Committee on Cancer (AJCC) Tumor–Node–Metastasis (TNM) staging is based on a comprehensive analysis of postoperative pathological findings. It should be used in predicting the prognosis and postoperative survival of patients (LoE 2; strong recommendation).

**Figure 2: Bismuth – Corlette Classification**

- Type I: Below the confluence of left and right hepatic ducts
- Type II: Reaching confluence, but not involving left or right hepatic ducts
- Type III: occluding common hepatic duct and involving either the right (IIIa) or left (IIIb) hepatic duct
- Type IV: Involving the confluence both right and left hepatic ducts; bilateral intrahepatic segmental involvement or multicentric
Assessment of Resectability

The cardinal principle defining resectability is presence of adequate functional hepatic parenchyma with achievement of negative resection margin along with ability to restore biliary flow in the absence of distant disease (57,82). Assessment of resectability should be done before any biliary intervention unless the patient is septic. Each case should be discussed in MDT and all hCCA cases should be referred to be managed at high volume specialist HPB centers (83,84).

Each patient’s clinical condition and performance status is assessed to ensure they can undergo major hepatic surgery (82). Cross sectional images are discussed in MDT meetings (85) for extent of biliary involvement, possibility of R0 resection, anatomical variations in hilar structures, quality of hepatic parenchyma and volume of the intended future liver remnant (FLR) (82). Adequate remnant liver is generally considered as 25% in normal parenchyma (86) while, in steatotic and cholestatic livers the safe limit is 30-40% (57,82,86). Inadequate remnant liver may necessitate FLR modulation (12,57,82,87).

Irresectability is defined based on the following parameters:

a) Metastatic spread: Once the disease has spread to distant organs, peritoneum and distant lymph nodes (57,82).

b) Patient factors: When patient is not fit to undergo major liver surgery due to comorbid medical conditions or has a cirrhotic liver with portal hypertension (57,82)

c) Local factors: There is no consensus regarding local factors determining irresectability (87), hence requiring consideration of individual patient characteristics in MDT discussion (85). However following criteria makes disease unresectable (57,82):

1. Bilateral hepatic duct involvement up to secondary biliary radicals
2. Encasement/occlusion of the main portal vein
3. Encasement of portal vein branch with atrophy of contralateral hepatic lobe
4. Hepatic duct involvement up to secondary biliary radicals with atrophy of contralateral hepatic lobe

Recently several reports (12,82,87–89) have shown improved survival in patients with locally advanced disease undergoing major hepatectomies, with portal venous or arterial resection and extended liver resections as right and left trisectionectomies. However, such resections should be performed in highly selected individuals (57). Portal vein resection is associated with survival advantage (87,89). While clinical benefits of arterial resection for patients with arterial invasion are still unclear (87), this technique results in higher rate of R0 resection (90).

Recommendations

- The assessment of disease resectability should be done as a part of hepatobiliary multidisciplinary team meetings, looking at biliary involvement, lobar atrophy, vascular involvement and future liver remnant (LoE2; strong recommendation).
Portal Vein Embolization
Most studies have reported that PVE induces significant hypertrophy of the future liver remnant (FLR), thereby increasing the chance of curative resection(91). The magnitude of FLR hypertrophy varies depending on the extent of liver disease and the technique of PVE(92). While PVE is generally considered safe, there is a risk of liver failure and other complications, especially in patients with poor liver function or extensive disease. A meta-analysis including 37 publications and 1140 patients undergoing PVE, showed liver hypertrophy by an average of 8-27%, with a complication rate of around 3% and zero mortality(93,94). Some studies have suggested that PVE may be associated with an increased risk of tumor progression or recurrence(95). Still, the evidence is conflicting, and the exact mechanisms of this effect still need to be fully understood.

The PVE should only be considered in patients who can achieve resectability with liver hypertrophy(96). The PVE should be performed early enough to allow for adequate FLR hypertrophy but not too early to allow tumor progression(96).

Segment-IV branch PVE can further improve left lateral segment hypertrophy and allow extended resection. However, it comes with a risk of reflux of embolic material to Segment II-III (FLR) portal veins. An alternative would be to perform liver venous deprivation with right and middle hepatic vein embolization at the same time. Early results from ongoing Hyperlive01 trial are encouraging (97). Patients should be monitored closely after PVE for potential complications, including liver failure, portal vein thrombosis, and infection. Imaging should be performed to assess the extent of FLR hypertrophy and monitor tumor progression. There is no clear consensus regarding the timing of the scan, but a 4–6-week window is preferred.

Based on the current evidence, PVE should be considered as a treatment option for patients with hCCA who are not suitable for upfront curative resection but have a chance of achieving resectability with liver hypertrophy. After PVE, if the FLR remains <20%, liver resection is deemed to be contraindicated.

In case of biliary dilatation, biliary drainage should be performed before embolization(98). Further research is needed to determine the optimal technique of PVE, the predictors of FLR hypertrophy, and the effect of PVE on tumor progression and survival outcomes.

Recommendations

- Portal vein embolization should only be performed in patients who can achieve resectability with liver hypertrophy (LoE 2; strong recommendation).
- Portal vein embolization should be considered In patients whose future liver remnant is less than or equal to 20% of total liver volume (LoE 2; strong recommendation).
- In patients with biliary dilatation of the future liver remnant, a biliary drainage catheter should be placed before portal vein embolization (LoE 2, recommendation strong).
Preoperative Biliary Decompression

Liver resection for hCCA carries mortality rates between 6.2% and 15%, with postoperative morbidity touching around 60% in Western studies (99–102). Mortality is linked to postoperative hepatic insufficiency and sepsis which develops in the compromised liver by previous jaundice, cholangitis, and malnutrition (101–103). The role of preoperative biliary drainage (PBD) in hCCA remains debated. The PBD improves coagulopathy, alleviates renal insufficiency associated with liver failure and provides symptomatic relief (104). The PBD reduces the risk of cholangitis and postoperative liver failure (105). However, on the contrary, cholangitis represents the most important complication related to PBD and is an independent prognostic factor for postoperative mortality (99,103,106,107).

While certain centers propose PBD until the serum bilirubin level descends below 2-3 mg/dl, optimal bilirubin levels before surgical resections remain variable across centers (57,108–111). She et al. reported a cut-off preoperative bilirubin level of >4.39mg/dl was associated with more hospital deaths (50% vs. 8.5%; p = 0.004), and 90-day mortality (50% vs. 9.8%; p = 0.008)(112).

Biliary drainage of the FLR helps restore metabolic and synthetic liver function and minimizes the potential risk of atrophy due to chronic cholestasis. A study involving 287 patients at Memorial Sloan Kettering Cancer Center and the Academic Medical Center in Amsterdam, also showed improved outcomes after PBD in patients with an FLR <30%(100). Major liver resection in 86 jaundiced patients without PBD with a predicted FLR of <50% was associated with higher morbidity (55% vs 24%; p =0.04), mortality (23% vs 8%; p = 0.001) and postoperative complications (62% vs 19%; p = 0.003)(113). A meta-analysis assessing the efficacy of PBD in resectable hCCA involving 2162 patients favored PBD in patients with cholangitis, malnutrition (serum albumin < 3 g/dL), prolonged jaundice, and high serum bilirubin levels ≥15 mg/dl(114).

Endoscopic retrograde cholangiopancreatography and percutaneous transhepatic biliary drainage (PTBD) are the most used modalities to achieve PBD for hCCA. The selection of drainage modality depends on local expertise, disease complexity, patient’s fitness, and preferences. Felice et al. showed significantly higher failure rates of PBD at community hospitals than at referral centers (52.7% v 36.9%; P = .002)(115).

Kishi et al. reported a higher incidence of major postoperative morbidities (Clavien-Dindo grade ≥ III) in the PTBD (23%) vs. non-PTBD (3%) groups (P = 0.01)(116). Wiggers et al, in a prediction model, reported that Bismuth type 1 & 2 resectable hCCA can benefit from ERCP as a primary drainage modality, whereas Bismuth IIIa or IV HCCA and a total bilirubin level above 8.8 mg/dL may be considered for initial PTBD rather than ERCP(117). European Society of Gastrointestinal Endoscopy (ESGE) suggests that an MDT should decide the indication and route for PBD(118).

DRAINAGE, a multicenter RCT was prematurely terminated because of higher mortality (41% vs. 11%; p=0.03) and cholangitis (59% vs 37%) in PTBD than in endoscopic biliary drainage (EBD) groups (119). INTERCPT, another RCT was also prematurely terminated due to higher mortality rates (50% EBD versus 80% PTBD) (120).

Some studies advocate PTBD for its ability to drain specific liver sectors, though advancements in ERCP techniques enable sector-specific drainage in ERCP at experienced centers (121). The endoscopic approach facilitates enteral drainage resulting in improved nutritional status (122). Tumor seeding is another concern requiring meticulous planning for appropriate drainage modality. The PTBD was an independent risk factor for seeding metastasis in patients with resectable hCCA than EBD (123,124)]. A systematic review showed that EBD was superior to PTBD in the prevention of seeding metastasis (7.8% vs. 17.1%, OR = 0.27,95% CI 0.13~0.56, P < 0.001) (125).
Endoscopic drainage can be achieved by conventional plastic stents, the inside-stent (IS) technique, or endoscopic nasobiliary drainage. The latter is associated with fewer infectious complications but carries a greater risk of catheter dislocation. Data is scarce to recommend the utilization of fully covered self-expandable metal stents (FCSEMS) for PBD in resectable hCCA (126–131).

The optimal extent of drainage remains controversial, and perhaps functional liver volume is a better parameter to guide biliary drainage than placing unilateral or bilateral stents. Draining more than 50% of the liver volume is an independent factor contributing to improving hyperbilirubinemia with a lower incidence of cholangitis, and prolonged survival (132–134). The preferred drainage side remains the FLR for better peri and postoperative outcomes(102,135–139).

There is no consensus about the optimal duration between PBD and surgical resection. Cholestasis impairs hepatic regeneration and restoration of hepatic function may take 4–6 weeks after PBD(140). Multiple factors influence optimal timing of surgery, including improvement in bilirubin, cholangitis, nutritional status, etc. Time duration varies across centers, ranging from 1 week to 413 days between biliary drainage and surgery(114).

**Recommendations**

- Preoperative biliary drainage (PBD) of hCCA is not routinely recommended, unless indicated in jaundiced patients with any of the following conditions (LoE 2; strong recommendation).
  - Cholangitis
  - Need for neoadjuvant therapy
  - Preparation for portal vein embolization
  - Malnutrition, hepatic or renal insufficiency
  - Predicted future liver remnant volume of ≤ 30 % following surgery
  - Debilitating symptoms such as intense pruritus
- The indication and route for preoperative biliary drainage should be decided by a multidisciplinary team based on patient characteristics, institutional experience, and resource availability (LoE 3; strong recommendation).
- ERCP over PTBD is recommended for Bismuth types I and II while the combination of ERCP and PTBD or PTBD alone is recommended for Bismuth types III and IV hilar cholangiocarcinoma (LoE 3; weak recommendation).
- PTBD is recommended in patients with unsuccessful and/or insufficient endoscopic biliary drainage (LoE 3; strong recommendation).
Surgical Resection
Surgical resection is the only potentially curative treatment option with reported 5-year survival from 25%-40% in patients undergoing R0 resection (12,57). Survival drastically decreases with involved resection margins and lymph node involvement (57,141). Surgical resection should include complete excision of involved extrahepatic bile ducts with, ipsilateral hepatectomy, caudate lobe resection (82,109,142,143), lymphadenectomy (144), hepaticojejunostomy and vascular resection (82,142,144) and reconstruction if required, aiming to obtain negative margins (57,144–146). Limited resections of bile duct(s) are associated with increased recurrence and poor survival and are not recommended (142). Hepatectomy can include right and left hepatectomy to right and left trisectionectomies (12,82,142,144). The Standard treatment option for Bismuth I and II tumors is right hepatectomy, with right sided resection preferred due to proximity of right hepatic artery to bile duct and increased length of extrahepatic portion of left hepatic duct (147). Left hepatectomy alone or accompanied by arterial resection and reconstruction of right hepatic artery is considered in cases of insufficient functional hepatic reserve in case of right hepatectomy (90,148) with large studies showing comparable long term survival (84). The choice of resection in Bismuth III and selected cases of Bismuth IV is dictated by extent of biliary involvement, lobar atrophy, vascular involvement, side of biliary dominance and hilar anatomical variations with generally Bismuth IIIa and IV requiring right trisectionectomy and Bismuth IIIb and IV requiring left trisectionectomy.

Parenchymal sparing hepatectomies may be utilized in highly selected patients (82,142) as they are associated with increased risk of positive surgical margins and decreased survival (144). Concomitant pancreaticoduodenectomy may be included to obtain negative resection margins (146,149) as it can be accomplished with demonstrated safety in many reports and is associated with survival benefit (150).

Staging Laparoscopy: This modality may be employed to exclude metastatic disease and avoid futile laparotomy (82) but the practice remains optional (145).

Extent of lymphadenectomy: Regional lymphadenectomy should be carried out in all patients undergoing surgical resection (57,87,142,144,151). The 8th edition of the AJCC TNM staging system recommend dissection of at least 5 lymph nodes for accurate staging (151). The extent of lymphadenectomy remains controversial (151) with western studies recommending lymphadenectomy of the hepatoduodenal ligament (82), and the posterior of the pancreatic head, i.e., No. 12 and No. 13 lymph nodes (151) and inclusion of station 8 along common hepatic artery by Japanese studies (12,141).

Frozen section: Intraoperative frozen section analysis is preferable to obtain negative resection margins if further resection is possible (82,152).

Recommendations

- Surgical resection should be to offered to all potential candidates (LoE 2; strong recommendation)
- The tumor should be resected along with the involved biliary tree, ipsilateral hemi-liver and caudate lobe with the aim to achieve a margin-negative resection. (LoE 2; strong recommendation).
- Frozen section assessment of proximal and distal bile duct margins can be considered if further resection is possible. (LoE 3; strong recommendation)
- Hepatectomy with pancreaticoduodenectomy should be considered for positive resection margins. (LoE 2; strong recommendation)
- Hepatectomy with portal vein resection and reconstruction should be considered in case of portal vein involvement. (LoE 2; strong recommendation)
- Hepatectomy with hepatic artery resection and reconstruction can be considered in case of hepatic artery involvement. (LoE 2; weak recommendation)
at hepatic hilus and underlying parenchymal liver disease such as PSC(82,153). Earlier attempts to employ orthotopic liver transplantation for such patients resulted in very dismal results(153–156). This led to the development of combined protocols of neoadjuvant chemoradiation followed by liver transplantation in carefully selected patients (154). The well-known Mayo Clinic Criteria (157) uses neoadjuvant chemoradiation along with diagnostic, inclusion and exclusion criteria, resulting in improved patient selection(155) This was subsequently validated in a large multicenter cohort of 214 patients, using similar protocols of neoadjuvant treatment, and a 5-year recurrence free survival (RFS) of 65% was achieved (158,159). At present, several transplant centers have approved protocols for liver transplantation in hCCA (153,154,159,160) and patients fulfilling Mayo criteria, after completing neoadjuvant chemoradiation are awarded MELD exception points by UNOS in USA (158,159). On the contrary this therapeutic option is not utilized in UK, Germany and Japan (159) due to risk of recurrence under immunosuppression.

As discussed, the diagnosis of hCCA is challenging. In the setting of liver transplantation, the diagnosis of hCCA requires a dominant stricture of peri hilar ducts on imaging, and 1 or more of the following: positive endoscopic cytology or biopsy, fluorescent in situ hybridization polysomy, CA 19.9> 100 U/mL in the absence of obstructive jaundice. (155,158)

Liver transplantation with grafts retrieved from both cadaveric and living related donors have been employed successfully (82,84,153–155,158,159). Nevertheless, liver transplantation in hCCA is associated with higher rates of arterial and portal venous complications (156,159,161). The neoadjuvant chemoradiation protocol has been modified by omitting brachytherapy to minimize the risk of hepatic artery thrombosis (159). Successful liver transplantation may warrant use of aorto-hepatic conduits (161) and interposition grafts for portal vein reconstruction(155,156,158,159).

The outcomes of upfront liver transplantation for hCCA have been discouraging, with early recurrence and poor long-term survival (155,158,159). Though established (155,158,159,162), but variability is found in components of neoadjuvant chemoradiation protocols (159,163) and the ideal protocol is to be defined (159). However, a retrospective multicenter report from the European Liver Transplant Registry suggests that in carefully selected patients within the Mayo Clinic criteria, 5-year survival of 60% could be achieved without neoadjuvant chemoradiation (164), highlighting the significance of strict selection criteria (164). This merits further exploration in clinical trials (164,165).

### Recommendations

- When considering liver transplantation for hCCA, the diagnosis requires presence of a dominant stricture of peri hilar ducts on imaging, and 1 or more of the following (LoE 2; weak recommendation).
  - positive endoscopic cytology or biopsy
  - Positive fluorescent in situ hybridization polysomy (FISH)
  - CA 19.9> 100 U/mL in the absence of obstructive jaundice
- For unresectable hCCA within Mayo Clinic Criteria, liver transplantation can be considered after neoadjuvant chemoradiation. The neoadjuvant regimen should include a combination of chemotherapy and radiation (LoE 2; weak recommendation).
- Upfront liver transplantation can be carefully considered for hCCA, within the Mayo Clinic Criteria, if neoadjuvant treatment is not possible, only in centers with approved protocols (LoE 2; weak recommendation).
- Given the increased vascular complications, need for arterial and venous jump grafts (natural or synthetic) should be evaluated in preoperative liver transplant planning (LoE 2; strong recommendation).
dearth of randomized control trials providing high-quality data on use of adjuvant treatments. Some studies have shown lack of benefit of adjuvant treatment in low risk groups so these patients may be observed(166). Retrospective study from MD Andreson Centre (167) showed a 5-year survival of 36% and a locoregional recurrence rate of 38% in patients with positive resection margin or positive lymph nodes who received adjuvant chemoradiotherapy in comparison to 5-year survival of 42% and a locoregional recurrence rate of 37% in patients with negative resection margin and negative lymph nodes with no adjuvant treatment. A Korean study on patients who were treated with adjuvant radiotherapy showed 5-year survival of 36%, 35% and 0% in patients with negative margins, positive margins and with gross residual disease respectively (168). The BILCAP study(169) a randomized, controlled study showed in an intention-to-treat analysis, the median OS was 49.6 months (95% CI, 35.1 to 59.1) in the patient group treated with adjuvant capecitabine compared with 36.1 months (95% CI, 29.7 to 44.2) in the observation group (adjusted hazard ratio 0.84; 95% CI, 0.67 to 1.06). The protocol-specified sensitivity analysis, adjusting for minimization factors, nodal status, grade, and sex, the OS hazard ratio was 0.74 (95% CI, 0.59 to 0.94). The benefit of adjuvant therapy extended more to patients with margin-positive surgery and node-positive disease. Table 2 provides a concise summary of the relevant clinical trials(169–172)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample Size</th>
<th>Treatment</th>
<th>Control</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCOG1202, ASCOT</td>
<td>Phase 3</td>
<td>Total: 440 Cholangiocarcinoma 180</td>
<td>S-1*</td>
<td>Observation</td>
<td>3 Years OS 77.1% vs 67.6% (95% CI, 61-73.3%) 3 years RFS 62.4% vs 50.9% (95% CI, 44.1-57.2%)</td>
</tr>
<tr>
<td>BILCAP</td>
<td>Phase 3</td>
<td>Total: 447 Cholangiocarcinoma 284</td>
<td>Capecitabine x 6 months</td>
<td>Observation</td>
<td>OS 51.1 months vs 36.4 months (95% CI, 34.6 - 59.1%) RFS 24.4 months vs 17.5 months (95% CI, 18.6-35.9%)</td>
</tr>
<tr>
<td>ESPAC-3</td>
<td>Phase 3</td>
<td>Total: 196 Cholangiocarcinoma 96</td>
<td>Arm A: Gemcitabine x 6 months Arm B: FU/leucovorin</td>
<td>Observation</td>
<td>Median Survival 20 months vs 18 months vs 27 months Negative Study</td>
</tr>
<tr>
<td>SWOG S0809</td>
<td>Phase 2</td>
<td>Total: 79 Cholangiocarcinoma 53</td>
<td>Gemcitabine with Capecitabine x 4 followed by CCRT</td>
<td>N/A</td>
<td>Median OS 35 Months (R0, 34 months.: R1, 35 months)</td>
</tr>
</tbody>
</table>

*S-1 available only in Japan. OS: Overall Survival; RFS : recurrence free survival

Table 2: Clinical Trials of Adjuvant Treatment in Hilar Cholangiocarcinoma
Surveillance Protocols after Surgery/Transplantation

Prognosis and surveillance after surgical resection:
Recurrent disease after surgical resection of hCCA is a foremost concern and is associated with poor prognosis. The major determinants of recurrence are resection margin status and lymph node metastasis (173–175). Lymph nodal positivity and R1/2 resection are associated with early recurrence and poor survival outcomes (167). The 5-year overall survival (OS) after hCCA resection ranges from 20-42% (136,173–175,177–179). In a recent systematic review and meta-analysis, Liang et al. extrapolated numerous factors that have prognostic value in determining the RFS and OS (175). The proven independent risk factors of OS are: preoperative bilirubin levels (> 3 mg/dl), preoperative CA 19-9 levels (> 150 U/ml), tumor size (2-3 cm), major vascular invasion, T-stage of disease (T3/4), lymph nodal metastasis (N-stage), moderate to poor tumor differentiation (Grade 2 and 3), resection margin status, and perineural and lymphovascular invasion (173–175). Adjuvant chemotherapy has a positive impact on OS (175). In a large retrospective study, Komaya et al. found that 5-year OS and RFS were significantly better in R0 resection as compared to R1 resection groups (48.5% vs. 17.7% and 58.5% vs. 10.4% respectively) (177). Further in-depth analysis revealed that 5-year RFS in R0 resection group worsened as the number of poor prognostic factors increased (177). On the basis of these observations, patients may be classified into

1. High risk (R1 resection or R0 with one/more than one poor prognostic factors)
2. Low risk (R0 resection with no risk factor)

Recommendations

- For patients with resected, margin-negative hCCA with negative regional nodes, the following options are available based on local experience, available expertise and availability of drugs
  1. Fluoropyrimidine (5 fluorouracil or capecitabine) or gemcitabine-based chemotherapy (LoE 2; weak recommendation).
  2. Fluoropyrimidine-based Chemoradiotherapy (LoE 2; weak recommendation).
  3. Observation (LoE 2; weak recommendation)
- For patients with positive margins or positive regional lymph nodes include:
  1. Fluoropyrimidine- or gemcitabine-based chemotherapy (LoE 2; strong recommendation).
  2. Fluoropyrimidine-based Chemoradiotherapy (LoE 2; strong recommendation).
  3. Fluoropyrimidine or gemcitabine-based chemotherapy followed by fluoropyrimidine-based Chemoradiotherapy (LoE 2; strong recommendation).
Therefore, follow up visit and postoperative treatment may be formulated based on identification of high risk and low risk groups after hCCA resection. As high risk group has high chance of recurrence and poor OS, therefore; close surveillance is required (177). The follow-up visit should include assessment of clinical parameters, LFTs, tumor markers (CA 19-9) and imaging at 2-3 monthly intervals for first 2 years and then 6 monthly for up to 5 years. Imaging should include ultrasonography at each visit and contrast CT scan of chest and abdomen or MRI at 6 monthly intervals or when clinical parameters mandate. These patients should be discussed in (MDT) meetings for adjuvant chemoradiotherapy (CRT) for better outcomes (175). A low risk group should be followed 2-3 monthly intervals for first year, 6 monthly intervals for second year and yearly up to 5 years (180,181).

Prognosis and surveillance after liver transplantation:

Liver transplantation for unresectable hCCA in a selective cohort after neoadjuvant protocol demonstrates a promising overall outcome (155,158,180,182). Although, a significant body of literature demonstrates superior OS and RFS after liver transplantation for hCCA (155,156,158,162,182,183), recent meta-analysis demonstrates heterogeneity of these data in terms of patient selection (PSC vs. non-PSC hCCA) and inherent limitations in study designs and data analyses resulting in wide variability in results (184). Nonetheless, 5-year OS and RFS for patient undergoing liver transplantation after neoadjuvant protocol exceeds 50% and 65% respectively(158,184). Despite inconsistencies in outcomes, major factors responsible for disease recurrence and patient survival are response to neoadjuvant chemoradiation and residual disease in explanted liver (156,183).

In addition, main outstanding issues in patients undergoing liver transplantation after neoadjuvant protocol are vascular (late hepatic artery thrombosis:18.9% and portal vein thrombosis:37.8%) and biliary complications (anastomotic stricture:39.2%) as a consequence of irradiated porta hepatis (156,162). This evidence supports the necessity of robust surveillance protocols. Thus, in addition to usual post-transplant surveillance, high risk surveillance strategy for detection of recurrence should be used for should be employed for those that have undergone liver transplantation.

Recommendations

- High risk group (R1 resection or R0 with one or more than one poor prognostic factors) should be followed every 3 months with clinical examination, Ca 19-9 and ultrasound. The CT scan should be done every 6 months for up to 5 years (LoE 2; weak recommendation).
- A low risk group (R0 resection with no risk factor) should be followed 3 months with clinical examination, Ca 19-9 and ultrasound. The CT scan should be done 6 months for the first year and then annually up to 5 years (LoE 2; weak recommendation).
- Post-transplant surveillance should follow high risk protocol (LoE 2; weak recommendation).

Management of Advanced Metastatic Disease

Metastatic cholangiocarcinoma carries limited treatment options and has a poor prognosis. Systemic chemotherapy is the mainstay of treatment. Combination chemotherapy with cisplatin and gemcitabine has been the standard of care. It has shown an overall OS [HR,
0.64, 95% CI, 0.52-0.80; P < .001] and median progression free survival (PFS) [HR, 0.63, 95% CI, 0.51-0.77; P < .001] benefit compared to single agent Gemcitabine in ABC-02 trial(185). In patients with limited renal function, Oxaliplatin may be substituted for cisplatin(186). Addition of programmed death-ligand 1 (PD-L1) immune checkpoint inhibitor (ICI) durvalumab to cisplatin and gemcitabine in a phase three, randomized trial, TOPAZ-1 trial has shown improvements in OS (primary endpoint; HR 0.76, 95% CI 0.64-0.91), response rate and PFS compared to cisplatin and gemcitabine alone(178). Another similar study keynote-966, using pembrolizumab as an immunotherapy partner came to a similar conclusion. Hence this combination with ICI is considered the first line treatment for advanced biliary tract cancers (BTC) availability and cost of ICI is challenging in a LMIC, therefore on case basis these medicines can be discussed especially in patients who have high microsatellite instability or are PD-L1 positive.

Molecular analysis should be carried out before or during first-line therapy to evaluate options for second and later lines of treatment in advanced disease. Approximately 40% of patients with BTC harbor genetic alterations which are potential targets for precision medicine(188). Fibroblast growth factor receptor (FGFR) or isocitrate dehydrogenase 1 (IDH1) inhibitors may be incorporated for patients with FGFR or IDH alterations (189,190). Immunotherapy with immune checkpoint inhibitors has shown promise in a subset of patients with microsatellite instability-high or mismatch repair-deficient tumors (191). Palliative care should be integrated early in the treatment plan to address symptoms, improve quality of life, and provide psychosocial support. Close monitoring of treatment response and regular reassessment of the treatment strategy are essential, considering the dynamic nature of metastatic cholangiocarcinoma and the potential for subsequent treatment modifications or clinical trial enrollment.

### Recommendations

- Immune check point inhibitors are now incorporated in first line regimens and should be used depending on availability with gemcitabine and cisplatin in metastatic cholangiocarcinoma. (LoE 2; strong recommendation).
- In patients with FGFR alteration, FGFR inhibitors (e.g., pemigatinib) should be considered as second line therapy (LoE 3; weak recommendation).
- Early integration of palliative care, focusing on symptom management, quality of life improvement, and psychosocial support, is essential in the management of metastatic cholangiocarcinoma (LoE 3, weak recommendation).

### Palliative Care

Approximately 20%-30% of patients with hCCA are diagnosed at a stage when surgical resection can be offered. Furthermore, comorbidities preclude surgical resection in a significant number of patients. The median survival after resection can be up to 4 years and without resection is less than 1 year(192).

Supportive care helps patients meet the physical, practical, emotional and spiritual challenges of cancer. It is an important part of cancer care, especially after treatment has ended. The end of cancer treatment may bring mixed emotions. Even though treatment has ended, patients need help for pain, jaundice, loss of appetite, cholangitis, liver abscess and liver failure. Majority of these patients are candidate for palliative treatment (39,193–195). The main aim
of palliative treatment is to improve quality of life by minimizing the number of hospitalizations. One of the main goals of palliation is to eliminate the obstructive jaundice caused by the tumor and this can be achieved by PTBD or endoluminal stent therapy. Other locoregional therapies, such as photodynamic therapy, radiofrequency ablation, trans-arterial chemoembolization (TACE), drug-eluting bead TACE, selective intraarterial radiotherapy with 90-Y microspheres, and external beam radiation therapy, are available, but currently, no prospective, randomized controlled trials have shown a survival benefit with these therapies(196,197).

With all the recent advancements in interventional endoscopy and radiology, palliative therapy for patients with advanced hCCA is still suboptimal. Ashat et al. reported that draining more than 50% of the liver volume is an important predictor of treatment effectiveness(198,199). Given the significant morbidity and mortality related to recurrent cholangitis, meticulous optimization of biliary drainage is critical to improving survival rates in patients with advanced stage hCCA.

Superiority of Self-expanding metal stents (SEMS) compared to plastic stents in unresectable hCCA has been observed in several studies(200,201). In a metanalysis SEMS had a lower risk of stent occlusion from sludge compared to the plastic stent [RR (95% CI): uncovered SEMS vs. plastic stent, 0.09 (0.04–0.18); and covered SEMS vs. plastic stent, 0.17 (0.08–0.37)](202). Self-expanding metal stents are hence preferred in patients with life expectancy of > 3 months(203).

Majority of studies on the natural progression of hCCA without any cancer treatment are retrospective in design and the large number of the patients who were treated with only best supportive care (BSC) had advanced cancer with a poor performance status (performance status 3-4)(192,204,205). In a Korean study on biliary tract cancers with BSC, the OS was 4.7 for intrahepatic, 9.7 for extrahepatic, 4.4 for gallbladder and 11.2 for ampulla of vater cancer. In multivariate analysis, variables associated with poor prognosis were metastatic biliary cancer [hazard ratio 2.19 (P = 0.001)], high baseline carcinoembryonic antigen level (defined as >4.0 ng/ml) [HR 1.51 (P = 0.024)] and high baseline CA 19-9 level (>100 U/ml) [HR 1.93 (P = 0.001)] (193).

**Recommendations**

- The attempt of palliative biliary drainage should be done at hepatobiliary centers. *(LoE 3; strong recommendation)*
- Biliary drainage offers significant survival benefit. The goal of drainage should be normalization and not just improvement of bilirubin levels. *(LoE 4; weak recommendation)*
- Self-expanding metal stents (SEMS) should be preferred for palliative drainage in those with life expectancy > 3 months *(LoE 3; strong recommendation)*.
- Patients who have advanced hCCA with high bilirubin and poor performance status of 3-4, should be offered supportive care *(LoE 2, strong recommendation)*.
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