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EASL Clinical Practice Guidelines on the management of extrahepatic cholangiocarcinoma☆,#

European Association for the Study of the Liver*

Summary

Recent years have witnessed significant advances in the imaging, molecular profiling, and systemic treatment of cholangiocarcinoma (CCA). Despite this progress, the early detection, precise classification, and effective management of CCA remain challenging. Owing to recent developments and the significant differences in CCA subtypes, EASL commissioned a panel of experts to draft evidence-based recommendations on the management of extrahepatic CCA, comprising distal and perihilar CCA. Particular attention is given to the need for accurate classification systems, the integration of emerging molecular insights, and practical strategies for diagnosis and treatment that reflect real-world clinical scenarios.

Introduction

Cholangiocarcinomas of the extrahepatic biliary tree comprise tumours arising within the extrahepatic biliary tree, which includes the gallbladder and the hepatopancreatic ampulla. Significant differences exist in the clinical presentation, molecular characteristics, and therapeutic management of gallbladder cancer, ampullary cancer, and extrahepatic cholangiocarcinoma (eCCA), with the latter further subdivided into perihilar (pCCA) and distal (dCCA).

Recognising these distinctions, the European Association for the Study of the Liver (EASL) appointed a panel of experts to draft evidence-based, clinically oriented guidelines specifically addressing eCCA, complementing the previously published intrahepatic cholangiocarcinoma (iCCA) guidelines.[1]

The diagnosis and management of pCCA and dCCA remain particularly challenging due to the anatomy of the biliary tree and the frequent late-stage presentation of these tumours. While advances in imaging techniques and molecular profiling have improved our understanding of pCCA and dCCA, differential diagnosis and precise tumour classification often remain difficult. This has significant implications for disease management and treatment strategies.

Surgical resection remains the only potentially curative option for eCCA; however, it is feasible in only 20-30% of cases due to late diagnosis and extensive local invasion at the time of presentation.[2] For patients with unresectable disease, systemic chemotherapy remains the standard of care. Emerging therapeutic approaches, including targeted agents for *HER2/ERBB2* amplifications and immune checkpoint inhibitors, have shown promising results but are applicable to only a small subset of patients.

This guideline adopts a pragmatic approach to address the diagnostic and therapeutic challenges associated with CCA classification and management. By synthesising current evidence on the anatomical, pathological, and molecular distinctions among CCA subtypes, we aim to provide clear, actionable recommendations for clinicians. Particular attention is given to the need for accurate classification systems, the integration of emerging molecular insights, and practical strategies for diagnosis and treatment that reflect real-world clinical scenarios.

Methods

The EASL Governing Board convened an expert panel to develop the current clinical practice guidelines (CPGs), ensuring a balanced representation in terms of gender, geography, and expertise. The panel comprised specialists in Pathology, Radiology, Endoscopy, Hepatology, Clinical Oncology, and Hepatobiliary Surgery. The CPG panel formulated questions using the PICO framework (Patient, Problem, or Population; Intervention; Comparison, Control, or Comparator; Outcome) across six core topics: Classification, Epidemiology, Surveillance/Early Diagnosis, Diagnosis/Staging, Therapy, and Follow-up. For each subtopic, two or three experts were primarily responsible for drafting the questions.

The PICO questions underwent evaluation by a Delphi panel consisting of 35 international experts. A 75% agreement threshold in the first Delphi round was required for question approval; questions falling below this threshold were revised

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Clinical Practice Guideline Panel: chair: Marco Marzioni; Secretary to the Chair: Luca Maroni; Panel members: Lars Aabakken (ESGE representative), Guido Carpino; Bas Groot Koerkamp, Julie Heimbach, Shahid Khan, Angela Lamarca, Anna Saborowski, Valérie Vilgrain, EASL Governing Board representative: Jean-Charles Nault

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and subjected to further evaluation in subsequent rounds. Approved PICO questions then provided the operational framework for comprehensive literature reviews conducted by the expert panel. Based on these reviews, one or more recommendations were formulated for each PICO question.

The quality of evidence was assessed following the Oxford Centre for Evidence-based Medicine (OCEBM) framework, adapted from the Oxford 2011 Levels of Evidence (Table 1). Recommendations were categorised as either strong or weak, in alignment with the OCEBM grading system (Table 2). Recommendations for each subtopic were drafted by the same expert panel members who formulated the corresponding PICO questions, and these drafts underwent review and approval by the entire CPG panel during subsequent meetings.

A second Delphi round was conducted to vote on the recommendations and to gather feedback to refine the manuscript. Consensus was classified based on the following thresholds: strong consensus: ≥95% agreement, consensus: ≥75% to <95% agreement, majority agreement: ≥50% to <75% agreement, no consensus: <50% agreement. All recommendations achieved a consensus level exceeding 75%, the minimum threshold required for acceptance without major revisions. The final version of the CPGs was subsequently submitted to external reviewers before it was sent to the EASL Governing Board for final approval.

Classification

In patients with extrahepatic biliary tract neoplasms, should the term extrahepatic cholangiocarcinoma/eCCA exclude malignant neoplasms of the gallbladder, the cystic duct and the ampulla of Vater?

Recommendation

- The term extrahepatic cholangiocarcinoma/eCCA should indicate malignancies arising from hepatic ducts (right, left and common) and the bile duct (frequently referred to as the common bile duct or ductus choledochus). The term "biliary tract cancer" should be used as a wide definition comprising all malignant neoplasms arising from the biliary tree, including intrahepatic CCA, extrahepatic CCAs, and gallbladder and ampullary carcinoma with biliary differentiation **(LoE 5, strong recommendation, strong consensus).**

From an anatomical point of view, the extrahepatic biliary tree comprises the hepatic ducts (left, right, and common hepatic ducts), the gallbladder and the cystic duct, the common bile duct (choledochus), and the hepatopancreatic ampulla.[3,4] In keeping with that, biliary tract cancers are currently classified into pCCA (from the hepatic ducts), dCCA (from the common bile duct), gallbladder carcinoma (from the gallbladder), cystic duct neoplasm (from the cystic duct), and neoplasms of ampulla of Vater (from the hepatopancreatic ampulla).[5]

Gallbladder carcinoma has peculiar clinicopathological features compared to pCCA and dCCA with well-established predisposing conditions, environmental exposures, and lifestyle behaviours.[6,7]

Malignant neoplasms arising from the hepatopancreatic ampulla are rare gastrointestinal malignancies and are included under the term biliary tract cancers. Histologic classification, biologic behaviour, clinical course and management of these malignancies slightly differ from those of pCCA and dCCA.[8]

In view of the impending new ICD classification, should the sub-classification and recording of CCA be bipartite (intrahepatic vs. extrahepatic), or tripartite (iCCA vs. pCCA vs. dCCA)?

Recommendation

- Given the significant differences in pathobiology, clinical presentation and management, the sub-classification and recording of CCA should be tripartite (iCCA *vs.* pCCA *vs.* dCCA) **(LoE 5, strong recommendation, strong consensus).**

In clinical practice, CCAs are typically classified into three subtypes according to their anatomical site of origin: intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA), with pCCA and dCCA often collectively referred to as eCCA. iCCA by definition arises within the liver parenchyma, proximal to the second order bile ducts and comprises the second most common form of primary liver cancer globally, after hepatocellular carcinoma. pCCA arises between the second-degree bile ducts and the insertion of the cystic duct into the common bile duct, whereas dCCA is confined to the common bile duct below the cystic duct insertion.[9] Historic studies report that pCCA accounts for around 50-60% of all CCAs, and iCCA

Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine.

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised-controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	RCT or observational studies with dramatic effects; SR of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Non-randomised-controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study)	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
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

Table 2. Grades of recommendation.

Grade	Wording	Criteria
Strong	Shall, should, is recommended. Shall not, should not, is not recommended.	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested. May not, is not suggested.	

accounts for less than 20% of CCAs.[10] These three CCA subtypes are heterogenous and can vary in their respective clinical presentations, risk factors, routes to diagnosis and clinical management, as well as exhibiting distinct epidemiological, clinical, molecular and genetic characteristics[3] (Fig.1).

Multiple epidemiological studies have consistently reported increasing age-standardised mortality rates for iCCA and stable or falling rates for eCCA[11] (Fig. 2). However, an important limitation in CCA epidemiology studies is the unknown rate of pCCA specifically, as the main World Health Organisation (WHO) International Classification of Diseases (ICD) coding systems have historically lacked a specific code for pCCA, which has likely been mostly miscoded as iCCA in the past.[12] The lack of specific coding for pCCA is to be corrected in the latest version of the ICD,[5] but this will not help with clarifying historical rates of pCCA as distinct from iCCA and dCCA in prior studies. The fact that different countries adopt new versions of the WHO ICD coding system at different times, often years apart, will further make correct interpretation of new, and particularly historical data, more challenging. All patients with CCA should therefore be classified as intrahepatic, perihilar or distal CCA. This should be clearly recorded at the tumour board outcome discussion.[13]

Can molecular analysis be used to distinguish iCCA from perihilar/distal eCCA in patients with CCA?

Recommendation

- Genetic alterations cannot currently be used to distinguish iCCA from perihilar/distal eCCA **(LoE 5, weak recommendation, consensus).**

Perihilar and distal CCA have somatic genetic alterations in *TP53* (35-55%), *KRAS* (30-46%), *ERBB2* (3-9%), *SMAD4* (8-30%), *CDKN2A* (5-28%) and *ARID1A* (3-20%).[14–16] One to 4% of perihilar/distal CCAs have microsatellite instability.[15,17] The incidence of genomic alterations depends on the anatomical location of biliary cancer. *BAP1* mutations, *IDH1* mutations and *FGFR2* fusions are mainly identified in iCCA and are rarely present in perihilar and distal CCA (*IDH1* mutations in 6-29% of iCCAs *vs.* 0-5% of distal/perihilar CCAs, *FGFR2* fusions in 5-21% of iCCAs *vs.* 0-1% of distal/perihilar CCAs and *BAP1* mutations in 12-19% of iCCAs *vs.* 0-3% in distal/perihilar CCAs).[17–24] In contrast, mutations in *KRAS*, *TP53* and *SMAD4* are more frequent in perihilar/distal CCAs, even if 5-10% of iCCAs still have these genetic alterations.[18–23] Interestingly, two different subtypes of iCCA have recently been described, the small duct type and the large duct type. As described in detail elsewhere,[1] the small duct iCCA type is a histologically heterogenous tumour that frequently harbours *IDH1* mutations and *FGFR2* fusions; in contrast, the large duct iCCA type presents a glandular structure with mucine production and genetic alterations similar to pCCA/dCCA (*KRAS* and *SMAD4* mutations). CCAs developing in primary sclerosing cholangitis (PSC) have genomic alterations similar to perihilar/distal CCA, with very rare *FGFR2* fusions and *IDH1* mutations, suggesting that these tumours are mainly perihilar/distal CCA in accordance with the physiopathology of carcinogenesis involving chronic inflammation of the large bile duct.[25,26] Gallbladder cancers harbour genetic alterations such as *TP53* mutations (29-63%), *CDKN2A* alterations (6-21%), *ERRB3* mutations (9-12%), *ERRB2* mutations or amplifications (10-15%) and *KRAS* mutations (8-11%) but almost never *IDH1* mutations and *FGFR2* fusions.[27–29] Published studies often mix pCAA and dCCA under the term “extrahepatic cholangiocarcinoma” and few studies have specifically studied the different genomic alterations between pCCA and dCCA. Notably, *TP53* mutations are enriched in dCCA (40-75%) compared to pCCA (11-55%).[20,21] No studies have specifically assessed whether *BAP1* mutations, *IDH1* mutations or *FGFR2* fusions in biliary cancer should *per se* define iCCA. It is not known if the rare cases of perihilar/distal CCA with *BAP1* mutations, *IDH1* mutations or *FGFR2* fusion are “misclassified anatomically” in the iCCA group. Consequently, despite a strong association between *BAP1, IDH1* and *FGFR2* genomic alterations and iCCA, there is insufficient evidence to systematically use genetic alterations to distinguish iCCA from perihilar/distal eCCA. However, in doubtful cases, genetic alterations could be helpful in distinguishing iCCA from perihilar/distal eCCA (Table S1).

Epidemiology

Should the presence or absence of known risk factors be routinely recorded for CCA cases to monitor CCA epidemiology?

Recommendation

- Data should be routinely recorded for CCA cases, noting whether they have recognised risk factors, specifying those risk factors, or if no known risk factors are present **(LoE 5, strong recommendation, strong consensus).**

For over 20 years, there have been consistent reports of increasing CCA incidence and mortality rates globally, particularly for iCCA, while rates of eCCA have remained relatively static or even declined.[11,30–32] Rising CCA rates and differences in rates between countries are thought to relate to an interplay between host factors, including underlying liver disease and the patient’s genome, and exposure to carcinogenic risk factors.[9] The highest rates of CCA are observed in North East Thailand and surrounding areas, where the main risk factor is believed to be chronic liver fluke infection, most commonly with *Opisthorchis viverrine*.[32] In the Western world, where there

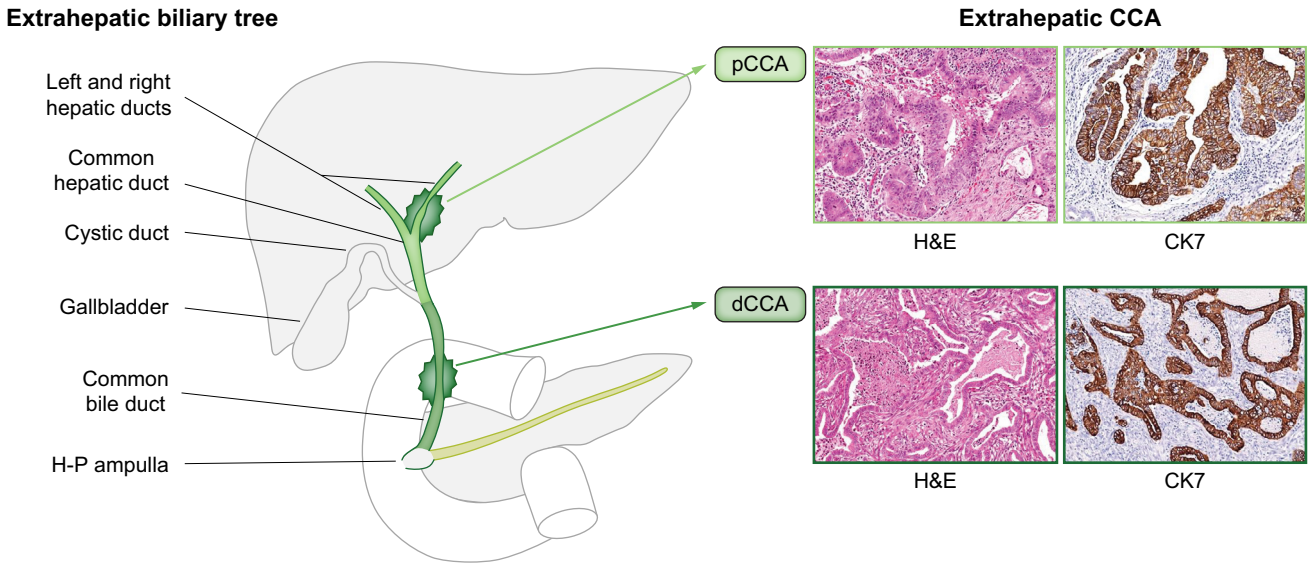

Fig. 1. Macroscopic classification of eCCA. The extrahepatic biliary tree includes the right and left hepatic ducts, the common hepatic duct, the common bile duct (choledochus), as well as the gallbladder, cystic duct, and hepatopancreatic ampulla. pCCA (light green) arises from the right or left hepatic ducts or the common hepatic duct (proximal to the cystic duct insertion). dCCA (dark green) originates from the common bile duct distal to the cystic duct insertion. AJCC, American Joint Committee on Cancer; dCCA, distal cholangiocarcinoma; eCCA, extrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma.

is no endemic liver fluke infection, CCA incidence is much lower (albeit rising). Liver flukes aside, other recognised predisposing factors for CCA certainly exist and are generally associated with chronic biliary and/or hepatic inflammation and progressive fibrosis. In the Western world, the commonest known risk factor for CCA is PSC.[3,9] Several risk factors are seemingly similar for both iCCA and eCCA, whereas others seem to be more specific for either iCCA or eCCA. Unlike hepatocellular carcinoma, wherein almost 90% cases occur on the background of chronic liver disease and cirrhosis, most patients

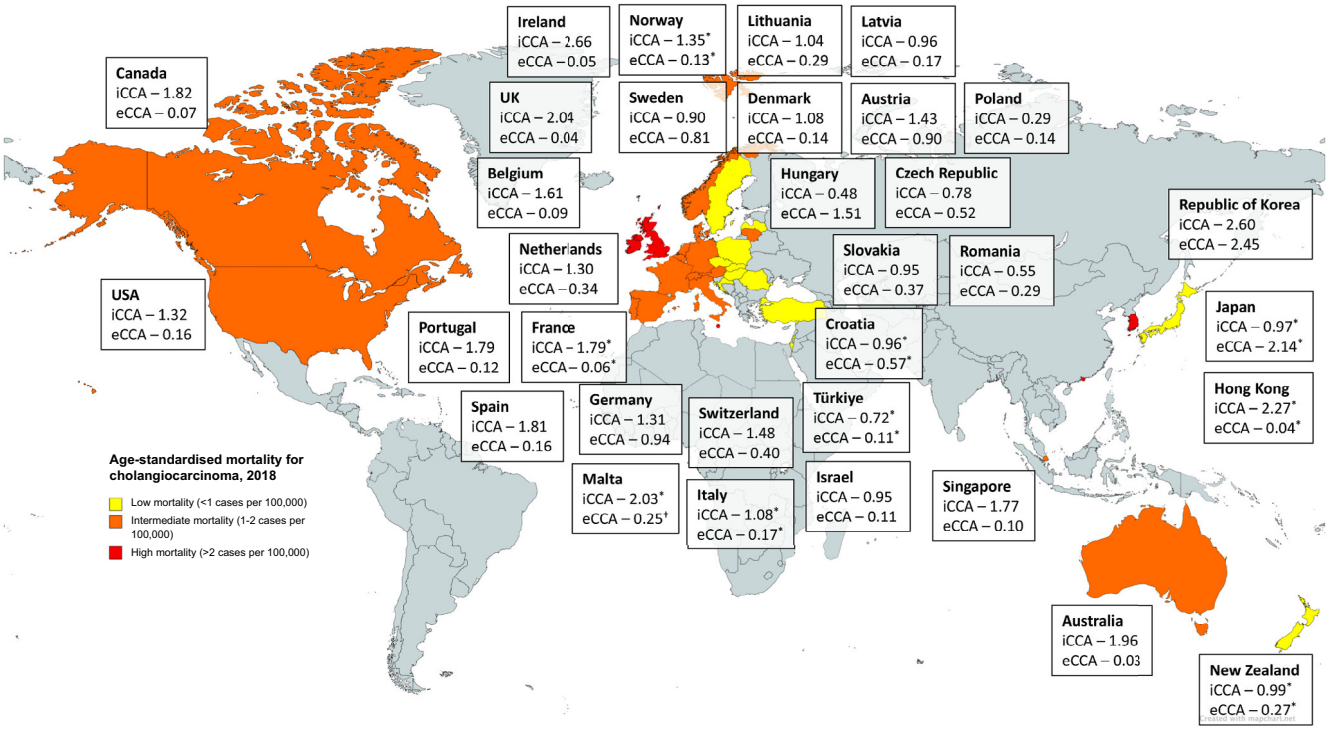

Fig. 2. Age-standardised mortality rates for iCCA and eCCA per 100,000 person-years. eCCA, extrahepatic cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma. *2016 data, †2014 data.

with CCA have no such history.[1,3,5,9] It has to be mentioned, however, that the presence of cirrhosis may be underreported, especially in iCCA, further supporting the importance of systematic reporting of risk factors.[33,34] Outside of liver fluke endemic areas, the majority of CCA cases are deemed "sporadic", with no recognised risk factor apparent in the patient's history. Although studies report rising rates of CCA globally, it is unknown if there are associated changes in rates of risk factors which may be contributing to these rising CCA case numbers.

Should selected patients with eCCA be considered for genetic counselling to identify hereditary cancer syndromes?

Recommendations

- Germline mutations testing and genetic counselling cannot currently be recommended for all patients with a diagnosis of pCCA and dCCA **(LoE 4, weak recommendation, consensus).**
- Patients with pCCA/dCCA and a personal and/or familial cancer history suggestive of hereditary cancer syndromes or with pCCA/dCCA with microsatellite instability or genetic alterations potentially linked with hereditary syndromes should receive genetic counselling with germline mutations testing as appropriate **(LoE 5, strong recommendation, strong consensus).**

No robust findings have demonstrated a reproducible association between single nucleotide polymorphisms and the risk of developing CCA.[35] Currently, no large-scale genome-wide association studies of CCA have been published, even if a large collaborative study is ongoing in the US. Furthermore, single nucleotide polymorphisms are typically associated with low odds ratios for cancer predisposition and are not currently used in clinical practice to stratify the risk of cancer development. Nonetheless, CCA is part of a spectrum of hereditary cancer syndromes, such as hereditary breast-ovarian cancer syndromes (associated with *BRCA1* and *BRCA2* germline mutations, as well as germline mutations in *ATM, CHEK2, PALB2*) and hereditary non-polyposis colorectal cancer syndrome known as Lynch syndrome, linked to mismatch repair deficiency, which results from mutations in *MLH1, MSH2, MSH6,* or *PMS2*.[36–38] Less commonly, CCA has been described in BAP1 syndrome, primarily associated with uveal melanoma and mesothelioma.[39,40] In all of these hereditary cancer syndromes, despite a higher incidence of biliary tract cancer compared to the general population, routine screening for CCA and gallbladder cancer is not recommended.[41,42] However, if a patient with CCA has a personal history of cancer and/or a familial history of cancer suggestive of these hereditary cancer syndromes, genetic counselling should be considered, possibly followed by germline cancer gene testing. Therefore, it is essential to systematically record personal and familial cancer histories in patients with pCCA and dCCA. Furthermore, genetic counselling may be recommended if microsatellite instability is identified in pCCA and dCCA to search for germline mutations in the mismatch repair system. Moreover, several studies have assessed the prevalence of germline variants predisposing to cancer in CCA and have identified germline mutations in 2% to 16% of patients. These mutations include variants in *APC, ATM, BAP1, BRCA1, BRCA2, FANCA, PALB2, PMS2, MUTYH, RAD51D, MLH1,* and *MLH2*.[43–48] Identifying *BRCA1/2* germline mutations could have implications for clinical practice, as CCA in these patients might respond to PARP inhibitors, radiation and platinum-based chemotherapy, although limited data are currently available for CCA.[49–51] Studies focusing on eCCA have identified mutations in genes such as *BRCA1, BRCA2, MLH1, MSH6, MUTYH, ATM, CHEK2, FANCA,* and *APC*[43–48] (Table 3). The penetrance of these cancer genes varies from low to moderate to high, and some mutations are of unknown significance. However, no study has clearly differentiated perihilar and distal

Table 3. Main studies involving germline mutations screening in CCA who include eCCA.

References	Number of patients with CCA (eCCA)	Country	Main germline variants in all CCA	Main germline variants in eCCA	Remarks
Okawa Y *et al.*[43]	1,292 CCA (569 eCCA)	Japan	5.5% of mutations including *BRCA1, BRCA2, PALB2, APC*, and *MSH6*	5% of mutations including *BRCA1, BRCA2,* and *MSH6*	
Uson Junior P *et al.*[44]	136 CCA (53 eCCA)	USA	16% of mutations including *BRCA1, BRAC2, ATM, MUTYH,* and *MLH1*	17% of mutations including *MUTYH, ATM, BRCA2, TP53, RAD51C,* and *CHEK2*	Low to high penetrance variants Significance of MUTYH mutations?
Yu H *et al.*[45]	265 CCA (194 eCCA)	China	7.6% of mutations including *BRCA2, ATM, RAD54L, BLM,* and *ERCC2*	5% of mutations including *BRCA2, ATM, CHEK2, FANCA, MLH1,* and *MSH6*	More germline variants in patients with a familial history of cancer
Maynard H *et al.*[46]	104 CCA (21 eCCA)	USA	15% of mutations *including BRCA1, BRCA2, MUTYH, BAP1, PMS2*, and *APC,* FH	19% of mutations including *APC, BRCA1, FH*, and *MUTYH*	Sometime high penetrance variant in patient without any familial history of cancer
Terashima T *et al.*[47]	182 CCA (106 eCCA)	Japan	2% of mutations including mainly *BRCA1* and *BRAC2*	1% of mutations including *BRCA1*	Method of analysis of germline mutations not clear
Lin J *et al.*[48]	639 CCA (164)	China	12% of mutations mainly *BRCA2* (n = 10), *MUTYH* (n = 9) and *BRCA1*	Not clearly reported	eCCA subgroup not clearly reported

The main germline variants identified in these studies were reported in this table.
The clinical significance of the germline variants is often difficult to assess in these studies.

in their analysis. Furthermore, all these series are retrospective analyses, lacking clear descriptions of personal and familial cancer histories, and genetic counselling was not performed in patients harbouring these mutations. Consequently, there is currently not strong evidence to support germline mutation testing in all patients with CCA.

Surveillance – early diagnosis

Which diseases should prompt surveillance for the early diagnosis of eCCA?

Recommendations

- In patients with PSC, regular surveillance should be performed to detect development of malignancy **(LoE 3, strong recommendation, strong consensus).**
- Patients with choledochal cysts should be operated on and subsequently undergo surveillance **(LoE 3, strong recommendation, consensus).**
- Patients with liver flukes should be treated, but a specific surveillance programme cannot currently be recommended owing to insufficient evidence **(LoE 4, weak recommendation, strong consensus).**

Given the dismal prognosis of established eCCA, identification, treatment and surveillance of precursor/precancerous conditions is of paramount importance.

eCCA is a rare disease, which makes research harder and evidence-based recommendations more difficult to define. Still, a number of conditions have been shown to increase the risk of lifetime development of CCA. Thus, an attractive strategy to reduce the impact of this cancer would be to focus surveillance on high-risk groups.

Primary sclerosing cholangitis carries an annual risk of CCA of 1.5-2.0%, a 400-fold increase from the general population.[52] This is on top of the increased risk of colorectal cancer in these patients, and mandates surveillance, ideally to identify premalignant lesions, since visible early-stage cancer already carries a poor prognosis. Several retrospective studies indicate a beneficial effect of surveillance programmes.[53–55]

Choledochal cysts are congenital malformations of the biliary system with prevalence varying from 1:100,000 in the West to 1:13,000 in Japan.[56] They are categorised according to the Todani classification based on location, shape and multiplicity. The cysts are considered premalignant, partially because of pancreatobiliary maljunction with reflux of pancreatic juice into the biliary tree. eCCAs are related primarily to Todani type I and IV cysts with sacculation or fusiform dilation of the extrahepatic bile duct, for which surgical resection is generally recommended, partially to mitigate malignancy development, but also to avoid the concomitant problems of biliary obstruction, stone formation or cholangitis.[57] However, the risk of malignancy remains even after resection,[58] with a recent meta-analysis reporting a median incidence of metachronous lesions of 5.6% but a range between 0.7% and 40%. This risk appears primarily limited to the first 20 years after resection,[59] although it is unclear whether these data would also apply to a western population. It appears reasonable to recommend some modality of surveillance after surgery in these patients, but given the uncertainties, it should be minimally invasive, *e.g.* liver biochemistry (for biliary obstruction), carbohydrate antigen 19-9 (CA19-9) and transabdominal ultrasound.[58] MRI should be considered when the patient has not undergone a pancreatoduodenectomy.

Liver flukes present the most significant risk factor for CCA in Southeast Asia,[60,61] whereas PSC dominates in the West. The predominant species are *Opisthorchis viverrini, Clonorchis sinensis, and Schistosoma japonica,* with *C. sinensis* being the most frequently diagnosed, but with regional variation. The pathogenesis appears to be partly explained by inflammation resulting from the interplay between flukes and biliary epithelium and partly by biliary obstruction and stasis caused by the flukes themselves. Immune responses to the flukes have also been implicated.

Active infection should be diagnosed and treated. However, serological indices of current or previous infection with flukes are frequent, and reinfection is common. Thus, a huge population is potentially amenable to surveillance, even after treatment. Ultrasound has been suggested as a logical modality for surveillance, but the overall utility in all individuals at risk has not been well established.

Other potential risk factors include ulcerative colitis (primarily via PSC even if undiagnosed) and gallstone disease. However, at the moment, given the low overall risk of eCCA development in these conditions, the lack of effective screening tools and resource limitations, specific surveillance protocols are not justified.

Precursor lesions in the bile ducts, namely biliary intraepithelial neoplasia, mucinous cystic neoplasm and mostly commonly intraductal papillary neoplasm of the bile duct frequently go unrecognised until transforming into cancer, unless targeted studies are performed to detect them at an earlier stage. Most of the risk groups listed above develop eCCA via these precursor changes, although *de novo* development is possible.

In patients at risk of eCCA development, which surveillance protocols should be used to improve outcomes?

Recommendations

- Patients with PSC should undergo annual ultrasound and/or MRI surveillance, with or without CA19-9 testing, with modifications according to relevant risk factors **(LoE 3, strong recommendation, consensus).**
- Patients with choledochal cysts and liver flukes may be followed after resection/treatment, with minimally invasive tests (biochemistry and ultrasound) **(LoE 4, weak recommendation, strong consensus).**

Surveillance must not only be directed at the appropriate risk groups but also be adapted to balance the risks/costs of the programme to the expected benefit. Being under surveillance is not without psychological costs as well.

In the West, PSC is the most thoroughly studied entity for surveillance. The diagnosis is not infrequently made in the early or even asymptomatic phase, and although 50% of cancers

occur within the first year, surveillance remains an ongoing challenge throughout the course of the disease, even after liver transplantation (LT). A recent study looked at follow-up of almost 3,000 patients in 27 European, US and Canadian centres.[55] A variety of modalities and schemes were followed but most centres employed a combination of CA19-9 and ultrasound and/or MRI as surveillance modalities, with intervals of 6-12-24 months for the various methods. Two centres used endoscopic retrograde cholangiopancreatography (ERCP) as part of the surveillance protocol. Altogether, CCA was detected in 5.9% of patients with PSC after a median of 7.9 years of follow-up, but an overall significant benefit on all-cause mortality was recorded, with a follow-up time of 1–19 years. Other retrospective series have reported somewhat similar results. However, stratification of risk has been largely lacking, mitigating the overall potential benefit of the programme. Prognostic scores have been suggested, but so far not validated across cohorts.[62] Also, no head-to-head comparison of various surveillance schemes has been published.

Patients with choledochal cysts should undergo surveillance after resection because of the risk of metachronous cancer. Recommended follow-up has been reviewed recently,[58] with a combination of liver function tests and CA19-9 annually for 20 years (then biannually), and ultrasound biannually for 20 years (then every 3 years).

Liver flukes: Follow-up and annual surveillance are generally recommended in these patients given the risk of re-infections and post infectious CCA development. Follow-up would likely be a combination of clinical checkup, liver tests and ultrasound, but no general recommendations are available based on the current literature. Also, the relevance of Asian data for a Western population is uncertain.

Diagnosis - staging

In patients with suspected pCCA or dCCA, which imaging modalities should be used for diagnosis?

Recommendations

- Contrast-enhanced CT and contrast-enhanced MRI should be used for the diagnosis of pCCA or dCCA as they are superior to ultrasound **(LoE 4, strong recommendation, strong consensus).**
- Contrast-enhanced MRI with magnetic resonance cholangiopancreatography (MRCP) should be used to accurately assess the level and extent of the biliary obstruction as it is superior to contrast-enhanced CT (**LoE 3, strong recommendation, strong consensus).**

Patients may be referred either for non-specific symptoms related to cholestasis such as abdominal pain or discomfort, anorexia, weight loss, or to more specific ones such as pruritus and jaundice. Ultrasound or CT are often the first imaging modalities to be performed. They show dilated intrahepatic bile ducts and lack of communication between the right and left hepatic ducts in pCCA, while extrahepatic bile ducts are dilated up to the head of the pancreas in dCCA. Other imaging findings, such as crowding of bile ducts and lobar atrophy, may be seen in pCCA when tumour growth predominates in one liver lobe. Findings that distinguish dCCA from pancreatic adenocarcinoma include the lack of main pancreatic duct dilatation and the absence of pancreatic tumour. Most pCCAs and dCCAs are of the periductal infiltrating subtype, which appears as a short stricture that enhances over time on multiphasic CT and MRI. Therefore CT and MRI using extracellular contrast agents should include the delayed phase.[63] eCCA is hypointense on gadoxetic MRI obtained at the hepatobiliary phase. Less often, eCCAs have a polypoid subtype with well-defined endoluminal mass.[64] CT and MRI are superior to ultrasound to diagnose pCCA and dCCA. They both have similar diagnostic performance, yet using magnetic resonance cholangiopancreatography (MRCP) and long T2-weighted sequences help to identify biliary obstruction below the dilated bile ducts and accurately assess location and size of the stricture.[65–68] Diagnosis of eCCA is still challenging, as presumed extrahepatic biliary tumours, in particular perihilar biliary strictures raising suspicion for pCCA, have been shown to be benign in approximately 15% of cases on pathologic analysis after surgery.[69–71] There are many mimickers of eCCA; patient history, clinical and biological data, presence of associated imaging findings, and the type of biliary stricture may help to differentiate eCCA from other conditions, including benign ones.

The most common differential diagnoses are the benign conditions PSC and IgG4-related sclerosing cholangitis. The diagnosis of CCA in patients with PSC is even more challenging. Endoscopic techniques such as cholangioscopy and endoscopic ultrasound are indicated in doubtful cases, allowing for precise biopsies and ultimately increasing the characterisation of biliary strictures.[72]

If eCCA is suspected, it is preferable to perform imaging before stenting for biliary drainage, since the diagnosis may be more difficult in the absence of biliary obstruction and in the presence of artifacts related to the stent.

In patients with suspected pCCA or dCCA, should CA19-9 serum levels be used to support diagnosis and/or prognosis?

Recommendations

- The use of CA19-9 serum levels to support the diagnosis of eCCAs is not recommended **(LoE 2, strong recommendation, consensus).**
- CA19-9 serum levels can be used as a prognostic biomarker for overall survival in pCCA and dCCA **(LoE 4, weak recommendation, strong consensus).**

Diagnostic role

CA19-9 is one of the most studied serum biomarkers in CCA and has been indicated as a potential diagnostic biomarker. Systematic reviews indicate that CA19-9 serum levels show a good specificity but a low to moderate sensitivity.[73,74] CA19-9 serum levels tend to increase in biliary obstruction of various origins, possibly leading to false positive results; therefore, CA19-9 levels need to be interpreted with caution in the setting of biliary obstruction. CA19-9 serum levels show high variability

in evaluated studies and cannot be used in patients who are negative for the Lewis antigen (5–10% of the general population).

Remarkably, in a large multicentre observational study with around 1,000 patients with eCCAs (pCCA = 592; dCCA = 399), elevated CA19-9 serum levels (cut-off value: ≥37 IU/ml) were associated with an increased risk of advanced tumour stages.[75] Particularly, high CA19-9 values associated with the presence of locally advanced disease (pCCA) and metastatic tumour stage (pCCA and dCCA).

Regarding the role of CA19-9 in the diagnosis of CCA in individuals with PSC, we refer to recent EASL guidelines which recommend the measurement of CA19-9 as an additional diagnostic tool when cancer is suspected, but not for surveillance purposes.[76]

Prognostic role

Concerning the prognostic role of CA19-9, an observational study indicated that elevated CA19-9 serum levels were an independent prognostic factor for overall survival.[75] In pCCA, the prognostic role of CA19-9 was also supported by a recent systematic review and meta-analysis, which included a total of 45 studies involving 7,338 individuals with resectable pCCA.[77] Furthermore, in a retrospective study including unresectable pCCA (n = 572), elevated CA19-9 levels at presentation (>1,000 U/ml) were an independent poor prognostic factor for overall survival.[78]

In dCCA, retrospective studies individuated preoperative CA19-9 serum levels as an independent predictor of shorter overall[79–81] and disease-free survival.[82]

In patients with suspected pCCA or dCCA, should cyto/histologic confirmation be sought in all cases?

Recommendations

- It is suggested that all reasonable attempts be made to obtain an unequivocal histological or cytological diagnosis **(LoE 5, open recommendation, consensus).**
- When cytological and histological analyses are equivocal and inconclusive but there is a strong clinical suspicion, it is suggested to proceed with stage appropriate surgical treatment in potentially resectable lesions after a full discussion with the multidisciplinary team and the patient; chemotherapy or radiotherapy usually require the demonstration of tumoural tissue **(LoE 5, open recommendation, strong consensus).**

A definitive diagnosis of eCCA should be based on pathologic confirmation.[13,83] However, it can be difficult to obtain an unequivocal cytological and histological diagnosis. A major pitfall is the low sensitivity (nearly 45% in a series meta-analysis) of brush cytology.[1] Moreover, it should be noted that, in at least 10% of patients who underwent surgical resection for bile duct strictures diagnosed as malignant, the histological examination of resected specimens ultimately revealed benign lesions.[83]

At least two, and if appropriate more, attempts can be made to obtain a pathologic confirmation.[1,13,83,84] However, due to the risk of seeding, transperitoneal endoscopic ultrasound (EUS)-guided fine needle aspiration of the primary tumour should be avoided in cases where LT is being considered.[84]

It is important to consider that in some cases cytological/histological confirmation may not be achieved; in those cases, it is suggested that subsequent diagnostic and therapeutic steps are discussed with the multidisciplinary team and a decision reached together with the patient. In this setting, while it may be reasonable to proceed to surgery in a potentially resectable lesion, chemotherapy or radiotherapy usually require the demonstration of tumoural tissue.

In patients with suspected pCCA or dCCA, which preoperative procedure should be used to obtain cytologic/histologic confirmation?

Recommendations

- ERCP with brush cytology and, whenever possible, ERCP-guided endobiliary forceps biopsy is suggested as the primary tool for acquiring tissue in cases of suspected eCCA **(LoE 4, weak recommendation, consensus).**
- ERCP with cholangioscopy-directed biopsies is suggested when: i) previous ERCP sampling in suspicious lesions was negative and ii) competence in cholangioscopy is available in the centre or in an accessible referral hospital **(LoE 4, weak recommendation, strong consensus).**

Imaging, including cholangiography by MRCP or ERCP – or cholangioscopy, may offer compelling indications of malignancy, but in the preoperative situation, very few surgeons would be willing to intervene without tissue-based proof of malignancy.

Traditionally, ERCP with brush cytology has been the standard of care for the acquisition of tissue for definitive diagnosis (Fig. 3). However, the variable but mostly modest sensitivity of this method in most publications, typically around 40%, highlights the urgent need for superior alternatives. Despite the excellent specificity of brushing, we risk missing or delaying a diagnosis of malignancy at a still operable stage.

Standard brush cytology has been analysed by ASGE[85] summarising seven studies with an overall sensitivity of 0.43. Additional analysis of the material, particularly fluorescence *in situ* hybridisation, has shown some initial promise, but given the paucity of access to the method, the skills required for analysis, and the fact that only 80% of biliary cancers present the necessary chromosomal instability,[86] this method remains investigational in most units. The same holds true for a variety of options within mutational analysis and next-generation sequencing.

Direct, fluoroscopy-guided biopsy of extrahepatic lesions is frequently available, depending on access and other anatomical conditions. It is cheap, technically easy if feasible, and allows for regular histological sampling of tumours, as well as the lower part of stricturing processes. A meta-analysis of 10 studies concluded that such biopsies have a sensitivity of 0.52%.[85] However, the procedure is performed almost exclusively in conjunction with brush cytology, offering a joint sensitivity of 0.66%, with a modestly extended duration of the procedure of less than 4 minutes. Thus, if ERCP-guided endobiliary forceps biopsy is technically feasible, it seems reasonable to include.

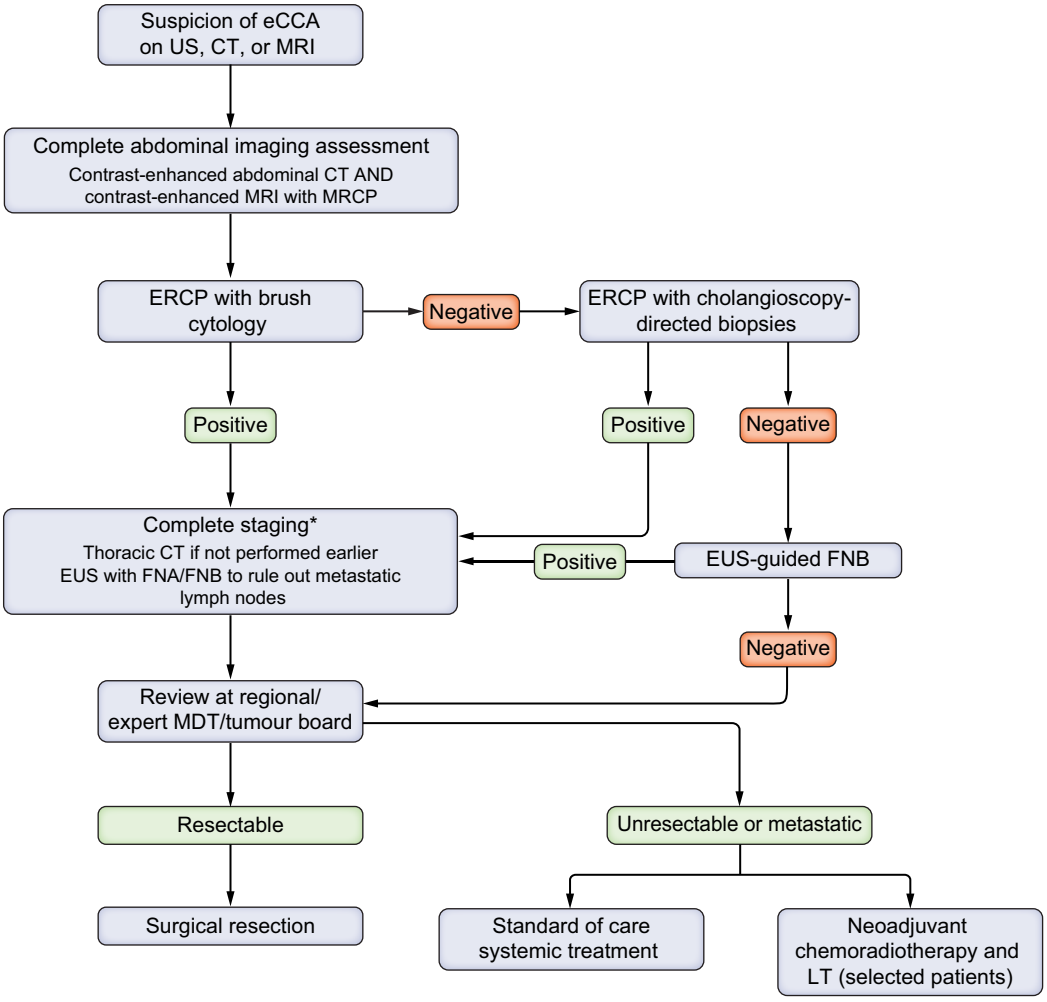

Fig. 3. Diagnostic algorithm for suspected eCCA. Patients with suspected eCCA should undergo thorough imaging evaluation, preferably before ERCP with stent placement. The recommended imaging approach includes: contrast-enhanced MRI with MRCP (preferred for assessing bile duct anatomy and tumour longitudinal extent) and Multiphasic contrast-enhanced CT of the thorax, abdomen, and pelvis (to evaluate hepatic artery/portal vein involvement and detect distant metastases). For definitive cytological or histological diagnosis, ERCP with brush cytology should be performed as the primary method of tissue acquisition. ERCP-guided endobiliary forceps biopsy should also be attempted whenever feasible. If initial methods fail or where expertise is available, cholangioscopy-directed biopsies may be used as an alternative or primary diagnostic tool. All cases of suspected eCCA should be reviewed by a multidisciplinary team at initial presentation and after imaging/endoscopic procedures. *Avoid trans-peritoneal biopsy if LT is being considered. eCCA, extrahepatic cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNB, fine needle biopsy; MRCP, magnetic resonance cholangiopancreatography; US, ultrasound.

Single operator cholangioscopy (Spyglass) offers a welcome opportunity for direct visual assessment as well as directed biopsies from biliary lesions, particularly amenable to extrahepatic lesions. In a summary analysis of 13 studies where cholangioscopy-directed biopsies were compared to brush cytology and/or ERCP-guided endobiliary forceps biopsy, the incremental yield of cholangioscopy-directed biopsies was 27%, with sensitivity increasing from 0.61 to 0.72. In a single randomised comparison between brush cytology and cholangioscopy-directed biopsies, sensitivity was 21.4% *vs*. 68.2%, with direct imaging also showing encouraging performance, but confirmatory studies are needed.[87] However, although the visual appreciation of a ductal lesion gives additional information, so far, the accuracy of interpretation in general has been inferior to histological analysis. This may pertain particularly to situations of pre-existing inflammation, or to lesions previously stented, which is frequently the case.

On the other hand, the introduction of cholangioscopy adds time, cost, and complexity, and it is still available only in select centres, adding to patient waiting times and inconvenience. Analysis of the microbiopsies obtained requires pathologists with specific skills and, particularly in the context of PSC, we still need more experience to understand the true added value. Finally, in distal strictures, access, as well as visualisation is complex and may limit the options for directed biopsies. Whether to include cholangioscopy as a primary tool or only after a negative brush/ERCP-guided endobiliary forceps biopsy remains to be determined, but in expert centres, cholangioscopy in the initial ERCP may possibly be cost effective.

Cytological/histological confirmation in eCCA can also be achieved with EUS-guided tissue acquisition (EUS-TA).[88] A number of studies and meta-analyses demonstrated a trend towards a better sensitivity of EUS-guided fine needle aspiration compared to ERCP with brush cytology or ERCP-guided

endobiliary forceps biopsy,[89–91] despite the difference not being statistically significant in all studies.[92,93] However, it has to be mentioned that no study specifically assessed the difference in diagnostic accuracy of EUS-TA between dCCA and pCCA, or compared it to cholangioscopy-directed biopsies. Moreover, EUS-TA has been associated with an increased risk of peritoneal dissemination in patients with pCCA subjected to LT;[94] therefore, this modality of tissue acquisition should be avoided in patients with pCCA who are candidates for LT and may be considered in patients with resectable pCCA and dCCA only when alternative techniques have failed.[95]

In patients with suspected pCCA or dCCA in which cytologic/histologic confirmation failed, should liquid biopsy or bile/plasma-based molecular analysis be considered for diagnosis?

Recommendation

- Liquid biopsies from bile or plasma are interesting future modalities for CCA detection but cannot currently be recommended beyond research and clinical trial settings **(LoE 4, open recommendation, consensus).**

Even with ductal tissue sampling techniques, a proportion of suspicious lesions in the extrahepatic bile duct remain undiagnosed, and the search for complementary techniques continues.

Aberrant DNA methylation alterations are valuable as biomarkers for a variety of cancers. In CCA, such markers have been identified both in plasma and in bile,[96] holding promise as an additional diagnostic modality in early stages of disease. In a recent validation study of 344 bile samples from 273 patients with no known risk factors and PSC-related CCA, as well as non-malignant controls, a panel of four markers showed very promising accuracy. In patients with PSC and a diagnosis of CCA within 12 months of sampling, the sensitivity was 100%, with a specificity of 90% (increased to 93% when only using patients with PSC and long-term follow-up as controls).[97]

A variety of other methylation panels have been suggested and tested, and the area is still part of the research agenda. Options for markers in plasma[98] or duodenal aspirate have been suggested but appear less promising. Currently and unsurprisingly, direct bile aspirate appears the most saturated medium for the relevant markers.

Extracellular vesicles (EVs), including exosomes, microvesicles, and apoptotic bodies, are small membrane-bound particles released by cells into the extracellular environment. In CCA, EVs play a significant role in tumour progression, metastasis, and intercellular communication by transporting proteins, lipids, and nucleic acids (*e.g.* miRNAs, mRNAs, and DNA) between cells. A number of EV-associated miRNAs, such as miR-21 and miR-191 have been shown to be elevated in patients with CCA and correlate with disease progression.[99,100] Moreover, aetiology-related logistic models, combining two to four serum protein biomarkers, with diagnostic and prognostic capabilities have recently been described.[101] The isolation and analysis of EVs from blood or bile provide a minimally invasive approach to detect CCA-specific signatures, offering a promising avenue for early diagnosis and monitoring.

In patients with pCCA or dCCA, which imaging modalities should be used for staging?

Recommendations

- Staging should be performed before any biliary stent placement. Multiphasic contrast-enhanced thorax-abdomen-pelvis CT should be used to assess hepatic artery and portal vein involvement and to look for distant metastases **(LoE 3, strong recommendation, strong consensus).**
- Contrast MRI with MRCP should be used to analyse bile duct anatomy and the longitudinal extent of the tumour **(LoE 4, strong recommendation, strong consensus).**
- In the setting of possible surgical treatment, EUS-guided fine need aspiration/biopsy of lymph nodes should be performed to rule out metastatic lymph nodes **(LoE 4, strong recommendation, consensus).**
- ^{18}F-fluorodeoxyglucose positron-emission tomography (FDG-PET) should not be used for the diagnosis and local staging of eCCA **(LoE 3, strong recommendation, strong consensus).**

Surgery with complete resection represents the only potentially curative treatment for eCCA.[102] Therefore, the goal of imaging is to determine surgical resectability and predict outcomes; correct staging is essential for this purpose. It includes the extent of the tumour in the biliary tree, the vascular involvement (arteries and veins), the direct invasion of adjacent structures, and the presence of lymph node metastasis, and distant metastases (the most common being liver, lung, and less commonly bones, adrenal glands, and the peritoneum). In pCCA, the volume of future liver remnant is also a key factor for surgical resectability. It is usually considered that future liver remnant volume of >25–30% is a safe cut-off for patients with healthy liver parenchyma, whereas >40% is used in patients with pCCA who typically present with longstanding biliary obstruction.[103] Precise terminology should be used and structured reporting of CT/MRI findings has been shown to provide more information than non-structured reporting.[104]

Vessels

Multiphasic contrast-enhanced thorax-abdomen-pelvis CT should include late arterial, portal venous, and delayed phases. Multiplanar, maximum and minimum intensity projection CT images may help evaluate the vessels, the tumour extent and bile duct anatomical variations. Vascular analysis is difficult as vessels are small, particularly the hepatic artery and its branches; consequently, prediction of vascular involvement on CT is more difficult for the hepatic artery than for the portal vein.[105]

Similar to the staging of pancreatic adenocarcinoma, precise descriptions of vascular involvement are required, such as the presence of a fat plane, abutment (less than 180°

circumferential contact), encasement (greater than 180°), occlusion, stenosis, and contour deformity. Absence of tumour-vessel contact has a very high negative predictive value, while stenosis or occlusion on CT is highly suggestive for arterial or venous involvement.

A meta-analysis demonstrated a pooled sensitivity of 89% and specificity of 92% for portal vein involvement, as well as 84% sensitivity and 95% specificity for hepatic artery involvement.[106]

Bile ducts

Regarding bile duct extension, tumour extension should be assessed upstream and downstream of the obstruction. In pCCA, analysis should focus on the primary biliary confluence as well as the right and left secondary biliary confluence. The presence of variant ductal anatomy should be searched for, as it may impact surgical resectability. CT with cholangiography may be used to define the biliary extent, yet MRI with long T2 single-shot and MRCP sequences may provide additional information.

Lymph nodes

Nodal involvement should be subclassified as regional (N1) and considered resectable if occurring along the cystic duct, common bile duct, proper hepatic artery, and portal vein, while periaortic, pericaval, superior mesenteric, or celiac artery lymph node metastases should be subclassified as N2 and considered unresectable.

Contrast-enhanced CT and contrast-enhanced MRI have low diagnostic performance for assessing perineural invasion and lymph node metastases.[107]

Comparison of CT *vs.* MRI

A large series has retrospectively reviewed contrast-enhanced (CE)-CT and CE-MRI with MRCP. A total of 214 patients including 121 with pCCA were included. There were no significant differences between CE-CT and CE-MRI regarding performance for assessing resectability. Yet, the AUC for determining resectability was higher when CE-CT and CE-MRI with MRCP were reviewed together than when CE-CT was reviewed alone in patients with discrepancies between the imaging modalities or with indeterminate resectability.[107]

EUS

EUS with or without fine needle biopsy has been shown to improve lymph node staging of eCCA. In a multicentre retrospective study, 14% of patients eligible for surgery with presumed resectable pCCA had metastatic lymph nodes identified by EUS. This percentage was higher in patients who had suspicious lymph nodes on cross-sectional imaging. Yet, when cross-sectional imaging did not detect any suspicious lymph nodes, EUS still changed clinical decision making in 6% of patients.[108]

PET

The role of FDG-PET/CT in eCCA is still debated. A systematic review and meta-analysis including more than 2,000 patients with biliary tract cancer has evaluated the diagnostic and staging performance of FDG-PET. The main drawback of FDG-PET is the lack of specificity (51.3%) for the diagnosis of CCA and the poor performance for determining nodal status. The performance is better for distant metastases.[109]

In patients with pCCA, which staging system should be used to guide therapeutic decision making?

Recommendation

- For patients with pCCA, the current American Joint Committee on Cancer (AJCC) TNM staging system is suggested **(LoE 4, open recommendation, strong consensus).**

Resectability has a major impact on outcomes and the performance of a staging system will be impacted by differences in practice that may impact resectability, such as in Asian populations *vs*. Western populations. The Bismuth system classifies pCCA according to the extension along the biliary ducts; the AJCC system classifies it according to the size of tumour extension into the liver parenchyma, whereas the Blumgart system combines the Bismuth classification of biliary duct involvement with features of the AJCC TNM classification, including extension into surrounding structures such as the portal vein and/or lobar atrophy.[110–112] Unlike the Bismuth or the Blumgart staging system, the AJCC system has been continuously updated. A recent Japanese single-centre retrospective analysis of 702 patients examined the three staging systems and found that the most recent AJCC TNM classification was a superior classification system for predicting resectability and survival in pCCA, though importantly, in this large series a high proportion of patients with advanced tumours (AJCC T4, Bismuth IV, or Blumgart T3) underwent resection[112] (Fig. 4).

Therapy

Should patients with (a suspicion of) localised (i.e. non-metastatic) pCCA be treated with surgical resection to prolong survival?

Recommendation

- Patients with localised pCCA should be treated with surgical resection if a complete resection (*i.e.* R0) is feasible with acceptable postoperative mortality **(LoE 2, strong recommendation, strong consensus).**

Surgical resection of pCCA is associated with 5-year overall survival rates of about 25-40% in nationwide and multicentre studies.[2,113–115] Five-year OS without surgical resection is extremely rare. Three-year OS with palliative systemic chemotherapy for advanced biliary cancer has been historically dismal (about 3% in the ABC-02 trial),[116] with a trend of improved 3-

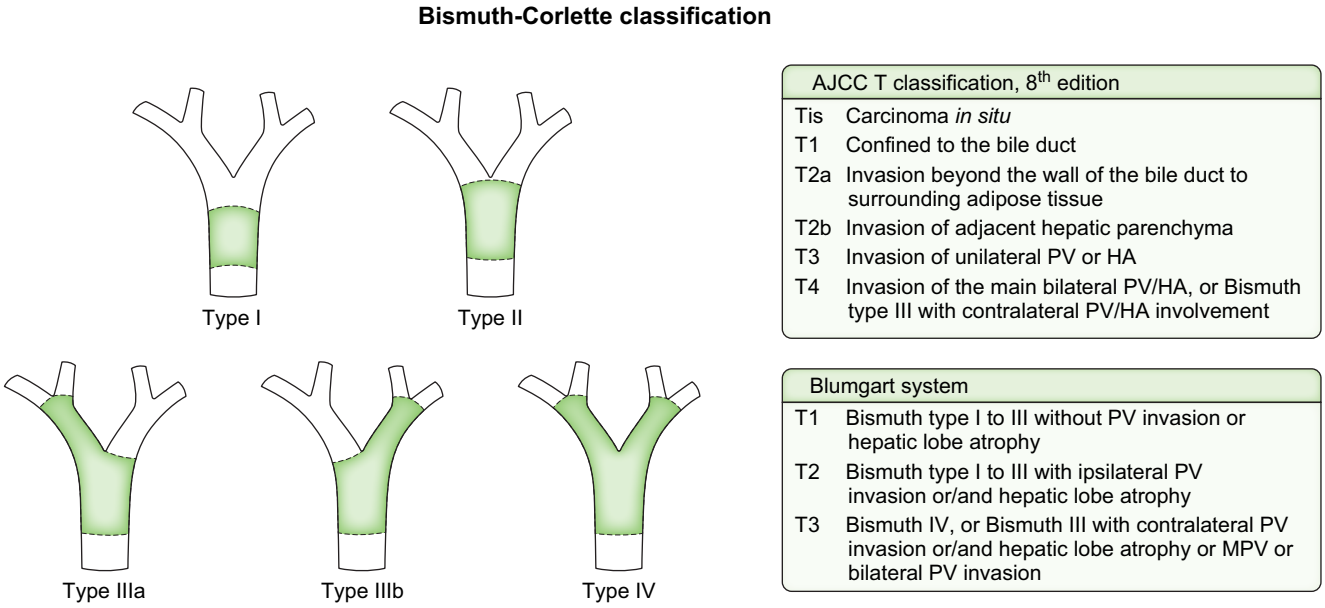

Fig. 4. Most used staging systems for pCCA. HA, hepatic artery; MPV, main portal vein; pCCA, perihilar cholangiocarcinoma; PV, portal vein.

year OS in most recent trials (about 14% in the TOPAZ trial).[117] In a nationwide study, 5-year OS without surgical resection was 1.8%.[2] In one study, the 3-year OS without surgical resection was 12%.[118] But a third of these patients had no pathological confirmation and only two patients lived beyond 5 years.

An incomplete resection (*i.e.* a margin-positive or R1 resection) is associated with worse survival (hazard ratio [HR] 2.5).[114] Patients with extensive biliary extent of disease (*e.g.* Bismuth IV) often require an extended hemihepatectomy to obtain a complete resection (*i.e.* a margin-negative or R0 resection). The other two independent poor prognostic factors after resection are positive lymph nodes and moderate/poor tumour differentiation.

The favourable 5-year OS of surgical resection of pCCA should be weighed against the high risk of postoperative mortality. The 90-day postoperative mortality is about 13% in expert centres.[119] Particularly extended resections leave a small future liver remnant with a high risk of postoperative liver failure and mortality. A combined risk model for both 90-day mortality and OS can identify patients that are unlikely to benefit from surgical resection.[120] Another study used machine learning to identify patients with resectable pCCA who had an expected "futile outcome".[121]

A preoperative tissue diagnosis of pCCA cannot always be obtained. The multidisciplinary team should be particularly aware of signs and symptoms of auto-immune cholangitis and stone disease.[122] The risk of a benign diagnosis at final pathology is about 10%.[123]

LT is an alternative treatment for localised pCCA. It is used particularly for patients with locally advanced (*i.e.* unresectable) disease. Five-year OS after LT is about 40-60%.[124] The majority of these patients have PSC. OS after LT may appear superior to surgical resection, but no randomised comparison has been published. Moreover, LT is a scarce resource.

Should patients with (a suspicion of) node-positive pCCA (N1) be treated with surgical resection to prolong survival?

Recommendation

- In patients with node-positive pCCA (N1), surgical resection can only be recommended if positivity is limited to perihilar lymph nodes and the anticipated postoperative mortality is acceptable **(LoE 3, weak recommendation, strong consensus).**

Positive locoregional lymph nodes are the strongest independent poor prognostic factor after surgical resection of pCCA (HR 3).[114] The 5-year OS rate of patients with node-positive pCCA was only 13% in a cohort of 12 expert centres.[125] This OS is clearly inferior to the 25-40% for all patients in nationwide and multicentre studies.[2,113–115] That said, the 5-year OS rate was only 3% in the same study for patients with localised disease who did not undergo a resection. The 3-year OS was 27% with and 7% without surgical resection. It appears that patients with node-positive pCCA may still live on average a bit longer after surgical resection than those receiving systemic treatment alone.

However, this potential benefit in OS should be weighed against the individual predicted postoperative mortality. A node-positive patient with a good performance status who requires a left hemihepatectomy should probably be considered for surgical resection. At the other end of the spectrum, frail node-positive patients requiring an extended hemihepatectomy should rarely be considered for resection. Nodal status is not always known before surgery. It can be assessed with EUS and fine needle aspiration preoperatively and with frozen sections intraoperatively.[108,126]

Many other poor prognostic factors for both OS and postoperative mortality are known. Preoperative models have been developed for both the individual predicted OS and individual

predicted postoperative mortality.[120] The short-term risk and long-term benefit of surgical resection should be discussed in the multidisciplinary team and with the patient.

Extraregional lymph nodes (*e.g.* aortocaval or truncal nodes) are considered distant metastatic disease (M1) in patients with pCCA (AJCC staging, 8th edition). These patients are only rarely considered for surgical resection.

Should patients with (a suspicion of) pCCA be treated with surgical resection if portal vein and/or arterial reconstruction is required to attain an R0 situation?

Recommendation

- Selected patients with (a suspicion of) pCCA may undergo portal vein or arterial reconstruction if required to achieve R0 resection **(LoE 3, weak recommendation, strong consensus).**

pCCA has a poor prognosis and surgical therapies remain the only curative option. Involvement of the hepatic artery and/or portal vein may preclude complete resection. Therefore, in specialised centres, vascular reconstruction has been proposed to improve surgical resectability, though there has been controversy about the impact of vascular reconstruction on survival. Song *et al.* performed a recent meta-analysis and determined that vascular reconstruction was associated with inferior survival. However, when the assessment was restricted to the most recent publications, portal vein reconstruction was shown to provide equivalent outcomes compared to those who did not require portal vein reconstruction.[127] Hepatic artery reconstruction remained associated with worse outcomes, compared to those who did not require vascular reconstruction, though those requiring such reconstruction are likely to have more advanced disease. A recent analysis of multi-institutional data from Western centres demonstrated that hepatic artery or portal vein reconstruction was not associated with inferior survival, though the numbers were relatively small.[128] The largest published single-centre analysis of the role of vascular reconstruction during resection for pCCA was recently published by Nagino *et al.*[129] This series of 1,055 consecutive patients demonstrated that patients requiring either hepatic artery (n = 146) or portal vein reconstruction (n = 157) had similar perioperative outcomes to those undergoing resection for pCCA without vascular reconstruction. While patients requiring hepatic artery reconstruction or portal vein reconstruction had inferior long-term survival compared to those who did not require vascular reconstruction (median 30 months *vs.* 61 months; p <0.0001), survival was better than in those who did not undergo resection (median, 10 months; p <0.0001). Survival was similar in those who underwent hepatic artery construction *vs.* portal vein reconstruction.

Should neoadjuvant chemoradiotherapy followed by LT be considered an option to improve outcomes in patients with unresectable pCCA?

Recommendation

- Neoadjuvant chemoradiotherapy followed by LT can be considered for selected patients with early-stage (T1-2 which are less than 3 cm, N0, M0) unresectable pCCA **(LoE 3, weak recommendation, strong consensus).**

LT alone for pCCA is associated with poor outcomes due to a high recurrence rate. Neoadjuvant chemoradiotherapy followed by LT for selected patients with early-stage, unresectable pCCA, is associated with 5-year survival rates of 60-70%.[130] Following a multicentre report from 12 US transplant centres that included 214 patients and demonstrated a 5-year disease-free survival rate of 65%, neoadjuvant therapy followed by LT has been adopted as a standard indication in the US.[130] It must be mentioned that, in this study, a confirmatory tissue diagnosis of malignancy from either brushing or biopsy was not obtained from all patients before enrolment in the protocol. Patients with early-stage, unresectable pCCA due to anatomic consideration or due to underlying PSC undergo careful assessment including cross-sectional imaging as well as EUS with biopsy of regional lymph nodes to rule out any evidence of metastatic disease. For patients with a perihilar mass, the mass must be ≤3 cm in radial diameter, though the length of extension along the bile duct is not an exclusion. The most recent single-centre series from the Mayo Clinic included 211 patients who underwent neoadjuvant therapy followed by LT and demonstrated a 5-year survival rate of 69%, and a 10-year survival rate of 62%.[131] A recent analysis of outcomes for 134 patients treated with neoadjuvant chemoradiotherapy followed by LT at 17 centres in Europe as well as North and South America demonstrated excellent outcomes. Disease-free survival at 5 years was superior when compared to a matched group of node-negative patients treated with resection (62% *vs.* 32%, p <0.001) over a similar time period (2014-2018).[124] Technical factors which may improve survival include avoidance of transperitoneal biopsy of the primary tumour, performing EUS with nodal sampling, a formal operative staging with biopsy of perihilar lymph nodes prior to LT, avoidance of hilar dissection during LT, and careful inspection of the vasculature for radiation injury with consideration of an arterial aortic jump graft to replace the native hepatic artery.[94,132,133]

Should the combination of gemcitabine, cisplatin and either durvalumab or pembrolizumab be considered standard of care for the first-line systemic treatment of patients with unresectable or metastatic eCCA to prolong survival?

Recommendation

- Gemcitabine and cisplatin in combination with either durvalumab or pembrolizumab should be considered standard of care for the first-line systemic treatment of patients with unresectable or metastatic eCCA **(LoE 2, strong recommendation, consensus).**

For nearly a decade, the combination of cisplatin (CIS) with the nucleoside analogue gemcitabine (GEM) was considered the standard of care for the first-line systemic treatment of biliary tract cancers, based on the ABC-02 trial in which the chemotherapy doublet demonstrated superiority over GEM alone.[116] In the TOPAZ-1 phase III trial,[117] a total of 685 patients with cancers of the biliary tract in the first palliative line of treatment, were randomised 1:1 to receive CISGEM, either in combination with the PD-L1-targeted antibody durvalumab or placebo. The immune checkpoint inhibitor combination

demonstrated superiority over CISGEM/placebo with a HR of 0.76 (95% CI 0.64–0.91) and a median OS of 12.9 *vs.* 11.3 months, and was subsequently approved for the first-line treatment of advanced biliary tract cancer by both the EMA and FDA. For patients with eCCA (n = 65 in the standard and n = 66 in the experimental arm) the HR was 0.61 (95% CI 0.41–0.91, updated analysis).

The concept of combining the chemotherapy backbone with an immune checkpoint inhibitor was further supported by the conceptually similar phase III Keynote-966 trial,[134] which randomised 1,069 patients with biliary tract cancers, and reported a HR for median OS of 0.83 (95% CI 0.72–0.95; one-sided p = 0.0034) favouring CISGEM plus the PD-1-targeted antibody pembrolizumab over CISGEM/placebo. The favourable HR for median OS with the immune checkpoint inhibitor combination was mainly driven by patients with iCCA (HR 0.76; 95% CI 0.64–0.91), whereas no clear benefit was demonstrated in the eCCA subgroup analysis (HR 0.99; 95% CI 0.73–1.35; n = 98 in the investigational arm and n = 105 in the control arm). The combination of CISGEM and pembrolizumab was also approved by the FDA and EMA for locally advanced unresectable or metastastic biliary tract cancers.

Although both pivotal phase III trials were stratified for primary tumour location (eCCA, iCCA and gallbladder cancer), interpretation of findings based on the site of origin should be viewed with caution, considering the overall low patient numbers especially in the eCCA and gallbladder cancer subgroups, and the *post hoc* nature of the subgroup analysis. Currently, no conclusive biomarkers predictive of response to the immune checkpoint inhibitor combination have been identified in the respective trials.

With regard to further intensification of chemotherapy by the addition of a third cytotoxic agent, the randomised phase III SWOG S1815 trial[135] addressed whether nab-paclitaxel improves OS when combined with CISGEM in the first palliative line of treatment, based on encouraging single-arm phase II data. The phase III study was, however, negative in the overall population. In an exploratory subset analysis, a favourable result was reported for patients with gallbladder cancer and in patients with locally advanced disease, but not for patients with eCCA.

In contrast, a Japanese randomised phase III trial (HBO1401-MITSUBA) reported a moderate, yet significant OS benefit for the triplet combination of CISGEM plus S1 *vs.* CISGEM alone, with a median OS of 13.5 *vs.* 12.6 mo (HR 0.791, 90% CI 0.628–0.996; p = 0.046).[136] Considering that the study included an all-Japanese population and that S1 is not readily available in non-Asian countries, as well as the positive phase III data and existing approval for the immune checkpoint inhibitor combinations, it is unlikely that this – or related – combinations will impact future trial design.

An irinotecan-based triplet therapy was tested in a randomised phase II setting. However, the Prodige 38 AMEBICA study, which aimed for a 20% 6-month progression-free survival (PFS) benefit under mFOLFIRINOX compared to CISGEM, was negative.[137] AMEBICA included 18 patients with eCCA in the mFOLFIRINOX and 20 patients in the CISGEM arm. Patients with eCCA reached a HR of 1.29 (0.65–2.57; p = 0.47) and, thus, the exploratory subgroup analysis did not suggest that patients with eCCA were more sensitive to mFOLFIRINOX than to CISGEM. Of note, subgroup analysis for iCCA patients indicated an advantage of CISGEM over the triplet (HR 0.58; 95% CI 0.39–0.85; p <0.01).

It is noteworthy that nanoliposomal-irinotecan (nalIRI) plus 5-FU/LV showed promising first-line activity in the phase II NIFE trial, meeting the primary endpoint of PFS rate at 4 months. The trial included a CISGEM arm as an internal randomised control, but was not powered for formal comparison of the two arms. Subgroup analyses suggested that eCCA and iCCA responded differently to the therapy, with a PFS benefit observed in the nalIRI over the CISGEM arm for eCCA (n = 25; HR for median PFS: 0.13; 95% CI 0.03–0.49) but not for iCCA (n = 66; HR for median PFS HR: 1.31, 95% CI 0.74–2.32).[138]

Should FOLFOX be considered standard of care for the second-line systemic treatment of patients with unresectable or metastatic eCCA without targetable alterations to prolong survival?

Recommendation

- In the absence of targetable alterations, FOLFOX should be offered as a subsequent line of systemic therapy for patients diagnosed with advanced eCCA who have tumour progression on first-line therapy. Alternatives to consider include irinotecan-based options (based on phase II trial data) **(LoE 2, strong recommendation, consensus).**

Upon progression to first-line chemotherapy, second-line chemotherapy options for biliary tract tumours include FOLFOX and liposomal irinotecan and 5-fluorouracil (NalIRI+5FU). The most robust data is available for FOLFOX, derived from the randomised phase III ABC-06 clinical trial from the UK,[139] which showed a benefit (even though modest) with FOLFOX (over active symptom control [ASC] alone), with median OS of 6.2 months (*vs.* 5.3 months; HR 0.69; 95% CI 0.50-0.97; p = 0.031) for the overall population. Within the ABC-06 clinical trial, a total of 162 patients were randomised. Of these, 19 and 26 patients diagnosed with eCCA were assigned to the ASC and the ASC+FOLFOX arm, respectively. Subgroup analysis for eCCA also reported a trend towards an OS benefit (HR 0.84; 95% CI 0.45-1.57).

NalIRI+5FU could be considered as an alternative to FOLFOX based on the NIFTY clinical trial, despite results not being replicated in the NALIRICC study. The South Korean phase II randomised NIFTY study identified a significant improvement on OS, in favour of NalIRI+5FU over 5FU alone (8.6 months *vs.* 5.3 months; HR 0.68; 95% CI 0.48-0.95; p = 0.02). For the eCCA population (22 and 25 randomised to NalIri+5FU and 5FU arm, respectively), OS benefit seemed to follow a similar trend (HR 0.87; 95% CI 0.56-1.34). For the NALIRICC study, HR for OS was 1.3 (95% CI 0.4-3.9) for the subgroup of 19 eCCAs included.[140–142]

Even though the benefit for eCCA may seem more modest compared to that for the overall population for both FOLFOX and NalIri-5FU, the number of patients in these subgroup analyses is small and statistical power limited. Based on this data, FOLFOX is recommended as second-line therapy. If standard

second-line therapy is not feasible or has been exhausted, NalIRI+5FU could be considered on a case-by-case basis, particularly if there is evidence of irinotecan sensitivity in the patient's tumour. However, negative results for OS and lack of robust evidence should be carefully considered.

Should molecular profiling be performed in patients with advanced dCCA or pCCA to evaluate the potential use of targeted therapies?

Recommendation

- Patients with unresectable or metastatic eCCA should receive molecular profiling to identify and therapeutically address actionable alterations and to support inclusion into clinical trials **(LoE 2, strong recommendation, strong consensus).**

Targeted therapies have been recognised as viable options in patients with biliary tract cancers. Because of the relatively low incidence and the small number of patients harbouring the respective targetable alterations, most of the evidence for precision oncology in biliary cancer stems from single-arm or basket phase II trials.

Currently, FDA and EMA approvals exist for futibatinib[143] and pemigatinib[144] in patients with *FGFR2* fusion/rearrangements, and, based on phase III data, for ivosidenib in *IDH1* R132 mutant biliary tract cancer.[145] Despite their relatively high frequency in iCCA, both *FGFR2* fusion/rearrangements and *IDH1* mutations occur only rarely in eCCA.

Positive phase II data further support $BRAF^{V600E}$ mutations[146–148] and *ERBB2* amplification/overexpression[149–156] as promising targets for precision oncology. A tumour-agnostic FDA approval exists for the combination of dabrafenib and trametinib in patients with solid tumours harbouring a $BRAF^{V600E}$ mutation, and who have progressed following prior treatment. For HER2 positive (IHC 3+) biliary cancers, the bispecific antibody zanidatamab has received FDA approval for patients with previously treated, unresectable or metastatic disease. Further, the antibody-drug conjugate trastuzumab-deruxtecan was granted tumour-agnostic FDA approval in adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumours who have received prior systemic treatment. Entity-independent EMA and FDA approvals exist for *NTRK*-fusion positive tumours (entrectinib[157] and larotrectinib[158]). Repotrectinib has been approved by the FDA and EMA for tyrosine kinase inhibitor-naïve and -pretreated solid tumours harbouring *NTRK* gene fusions, and a positive CHMP opinion (EMA) was issued in November 2024 for this indication.[159] In patients with advanced *RET* fusion-positive solid tumours, selpercatinib was approved by the FDA and EMA.[160] Of note, both *NTRK* and *RET* gene fusions are both generally infrequent in patients with CCA. Basket trials have also included $KRAS^{G12C}$[161,162] mutant biliary cancers, as well as rare biliary tract cancers with *NRG1* fusions.[163,164] Ongoing clinical trials are addressing, amongst others, KRAS non-G12C alterations, *FGFR2* amplifications/mutations, non-V600E BRAF mutations, *MTAP* deletions and *MDM2* amplifications.

Based on the few existing standard lines of therapy, available and emerging data for molecular targets in the phase II setting, and the challenges associated with recruiting patients with biliary tract cancers and rare alterations into genomically stratified trials, broad molecular profiling should be performed early on during first-line systemic therapy in patients with eCCA who are in sufficient physical condition to receive second- or further lines of therapy. Whenever targeted options are offered within the framework of clinical trials in earlier lines of therapy, profiling should be performed at an earlier stage of oncological treatment.

Should adjuvant systemic therapy with capecitabine be considered standard of care for patients after resection of eCCA to prolong survival?

Recommendation

- Adjuvant capecitabine should be offered to patients with resected invasive (excluding tumour *in situ*) eCCA regardless of T, N and resection margin status **(LoE 2, strong recommendation, consensus).**

Following surgery with curative intent, patients with resected CCA and gallbladder cancer (R0 and R1) should be offered adjuvant therapy in the form of single agent fluoropyrimidine.[165,166] Clinical trials exploring gemcitabine-based chemotherapy approaches failed to show any significant benefit,[167–171] thus remaining investigational (ACTICCA-1).

The phase III randomised BilCap clinical trial performed in the UK,[165] randomised patients to capecitabine or observation. Despite the fact that the BilCap study did not meet its primary endpoint of OS in the intention-to-treat population, capecitabine was adopted as standard adjuvant therapy based on a significant improvement of the OS in a pre-specified sensitivity analysis (53 months (95% CI 40-not reached) *vs.* 36 months (95% CI 30-44), HR 0.75 (95% CI 0.58-0.98; $p = 0.033$). Long-term follow-up data confirmed this benefit:[172] HR 0.74 (95% CI 0.59-0.94). Ikeda and colleagues explored S-1 *vs.* observation and reported similar findings in Japanese patients in the ASCOT study: adjusted HR for OS of 0.69 (95% CI 0.51–0.94); one-sided $p = 0.0080$).[166]

These two studies did report on the subgroup analyses for eCCA, with outcomes being specified for perihilar and distal CCA separately. For pCCA, a HR of 1.08 (0.68-1.71) and 0.84 (95% CI 0.47-1.51) were reported for capecitabine (n = 128) and S-1 (n = 87), respectively. For dCCA, these HRs were 0.70 (95% CI 0.47-1.06) and 0.75 (95% CI 0.45-1.25) for capecitabine (n = 156) and S-1 (n = 158), respectively.

Based on the data available, and despite the benefit for eCCA subgroups appearing to be more modest, which is likely to be due to the limited number of patients and reduced statistical power, adjuvant capecitabine is the treatment of choice in Western populations after R0 and R1 resection for eCCA.

A therapeutic algorithm is proposed in Fig. 5.

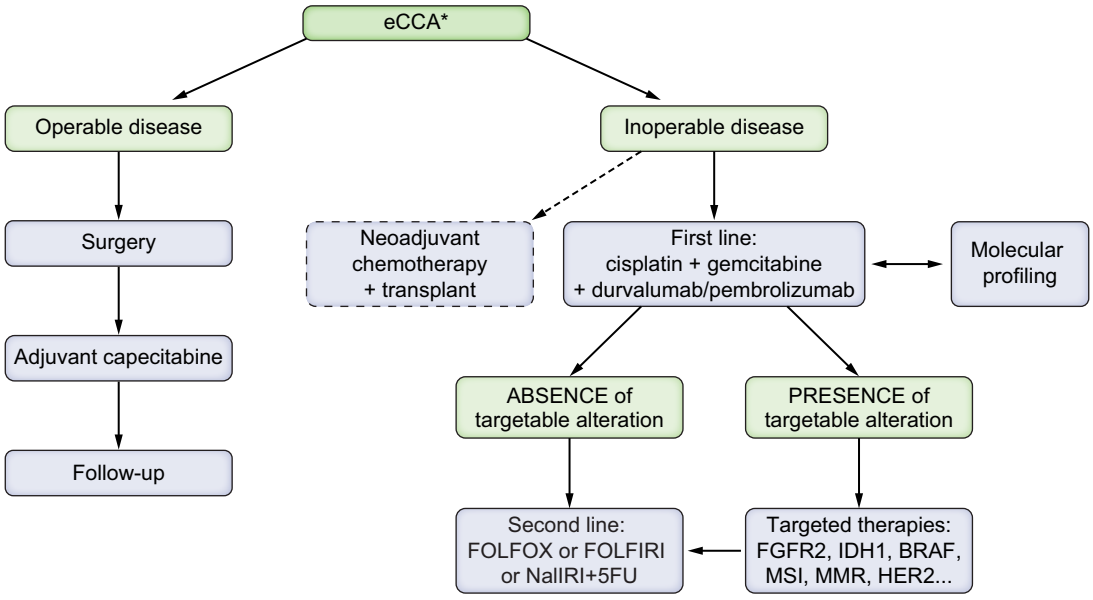

Fig. 5. Therapeutic algorithm for eCCA. All patients with non-metastatic eCCA should be evaluated for surgical resection if a complete resection (*i.e.* R0) is feasible with acceptable postoperative mortality. Those undergoing surgery should receive adjuvant therapy with capecitabine; chemoradiotherapy may be considered for individual cases, particularly in R1 resection scenarios. For patients with inoperable eCCA (unresectable or metastatic), the standard first-line systemic treatment is gemcitabine and cisplatin in combination with either durvalumab or pembrolizumab. Molecular profiling to identify actionable alterations and/or facilitate clinical trial enrollment should be offered to all inoperable patients. In the absence of targetable alterations, FOLFOX is recommended as second-line systemic therapy. Currently approved systemic options for targetable alterations are also available. eCCA, extrahepatic cholangiocarcinoma; MSI, microsatellite instability; MMR, mismatch repair.

Should adjuvant chemoradiotherapy after R0/R1 resection of eCCA be considered to prolong survival?

Recommendation

- Chemoradiotherapy cannot be recommended routinely after R0/R1 resection of eCCA, but it may be considered in individual patients with eCCA, especially in an R1 situation **(LoE 3, weak recommendation, consensus).**

Based on the per-protocol analysis of the phase III BilCAP study, capecitabine is currently recognised as the adjuvant standard of care. No prospective randomised-controlled trials (RCTs) have compared adjuvant chemoradiation *vs.* chemotherapy.

Retrospective studies suggest that chemoradiation may improve clinical outcome parameters, including survival, over no chemoradiation,[173] or may allow patients at high risk of locoregional recurrence (R1 or pN1) to achieve an OS comparable to those with lower risk of locoregional recurrence.[174] The OS benefit of adjuvant chemoradiation, especially in R1 patients, was also observed in a retrospective cohort that exclusively included patients with pCCA, and both adjuvant chemo or chemoradiation were superior to no adjuvant therapy in patients with R0 stage III-IVa.[175]

A 2012 meta-analysis aimed to assess the use of adjuvant therapy in biliary cancers and found a greater benefit of chemo- or chemoradiotherapy than radiotherapy alone (odds ratio [OR] 0.39, 0.61, and 0.98, respectively; $p = 0.02$). The analysis further supported the use of radiation in node-positive, and in margin-positive disease, with the benefit in margin-negative disease remaining uncertain.[176] A 2022 network meta-analysis also observed a benefit for adjuvant chemoradiation in patients with CCA, the majority being patients with eCCA.[177]

Recruiting between 2008 and 2012, and thus prior to communication of BilCAP, the single-arm phase II SWOG 0809 trial assessed GEM-capecitabine followed by concurrent capecitabine and radiotherapy in patients with eCCA (n = 54) or gallbladder cancer (n = 25), stage pT2-4 or nodal positive or positive resection margins, M0, and performance status 0-1, following radical resection.[178] With 2-year OS rates of 67% and 60% in R0 and R1 patients, respectively, the trial met its predefined primary endpoint (2-year OS rate >45%). However, based on the single-arm nature of the trial, the level of evidence is limited, and no strong recommendation can be made that supports the use of chemoradiotherapy over adjuvant capecitabine at this point.

In patients with eCCA amenable to surgical treatment, should pre-operative endoscopic or percutaneous biliary drainage be routinely performed to improve surgical outcomes?

Recommendations

- In patients with eCCA amenable to surgical treatment, routine preoperative biliary drainage should be avoided **(LoE 1, strong recommendation, consensus).**
- Preoperative drainage should be considered in case of cholangitis, renal failure, intractable pruritus, high bilirubin values, neoadjuvant chemotherapy, planned extensive surgery or expected long waiting time for surgery **(LoE 3, strong recommendation, strong consensus).**

Biliary obstruction is a significant component of the clinical situation in patients with eCCA, regardless of their surgical options. It was previously believed that relief of preoperative jaundice was a significant predictor of improved peri- and postoperative results. However, this has to be weighed against the risks associated with the drainage procedure itself. Recent data challenge the role of preoperative drainage for improving hyperbilirubinemia *per se*.

A high-quality randomised trial from the Netherlands compared preoperative drainage to early (<1 week) surgery for patients with malignant *distal* biliary obstruction. The authors found a significant increase in serious complications (74% *vs.* 39%), despite the drainage procedure being technically successful in 94%.[179] This was a study of periampullary tumours (including dCCA, cancers of the pancreatic head, and ampulla of Vater), but the results were replicated in a number of other RCTs, regardless of endoscopic or percutaneous approach.[180,181] A Cochrane review came to the same conclusion, summarising six trials with 520 patients. As did recent ESGE (European Society of Gastrointestinal Endoscopy) guidelines on biliary stenting.[182] Infectious complications appear to be the primary driver for the risk of drainage, while its beneficial effects are more difficult to ascertain. However, this depends on the waiting time for surgery, while already existing cholangitis due to biliary obstruction may also change the situation. Renal failure, excessive pruritus, and the need for neoadjuvant chemotherapy may also call for preoperative drainage, but this should always be discussed with the surgeon.[182]

Patients with pCCA differ from those with dCCA because they typically require a major hepatectomy. Moreover, portal vein embolisation is often required for an adequate future liver remnant. Portal vein embolisation is only possible after adequate biliary drainage. The minority (about 5-10%) of patients with pCCA who are eligible for a left hemihepatectomy may safely undergo a resection without prior biliary drainage.[183]

In patients with eCCA amenable to surgical treatment and an indication for biliary drainage, should endoscopic drainage be preferred over percutaneous drainage?

Recommendations

- In patients with dCCA amenable to surgical treatment with an indication for biliary decompression, endoscopic drainage should be preferred over percutaneous drainage **(LoE 3, strong recommendation, strong consensus).**
- In patients with pCCA amenable to surgical treatment with an indication for biliary decompression, endoscopic drainage cannot be recommended over percutaneous drainage owing to insufficient evidence **(LoE 3, weak recommendation, consensus).**

In the setting of distal biliary obstruction due to suspected dCCA, the endoscopic approach offers the advantage of combining both diagnostic (EUS-guided fine needle aspiration/biopsy; endobiliary sample acquisition during ERCP) and therapeutic (stent placement) potential.

Moreover, despite percutaneous transhepatic biliary drainage (PTBD) being technically feasible in the majority of patients, a number of retrospective studies have demonstrated a negative impact on the prognosis of patients. PTBD is associated with a higher incidence of peritoneal and hepatic metastasis and lower rates of 5-year disease-free survival.[184–186]

The management of biliary obstruction in patients with resectable pCCA remains more controversial.

A recent meta-analysis of 16 studies evaluating the success rate of endoscopic biliary drainage (EBD) and PTBD in the setting of malignant biliary obstruction found no statistical differences between the two procedures. ERCP procedures seemed to be associated with a lower rate of complications and shorter hospital stay compared to PTBD procedures.[187] In a similar meta-analysis involving 17 studies, the evaluation was conducted according to the resectability of pCCA. In resectable pCCA, the meta-analysis confirmed a similar technical and clinical success rate between ERCP and PTBD and a lower number of days in hospital stay for EBD; however, post-drainage complications and post-drainage pancreatitis were significantly less frequent in the PTBD group.[188]

The only available prospective randomised trial evaluating the number of severe complications in an unselected population of patients with potentially resectable pCCA subjected to EBD or PTBD was prematurely terminated due to higher all-cause mortality in the percutaneous group. Despite this limitation, severe drainage-related complications occurring prior to surgery were similar between EBD and PTBD (63% in the PTBD group *vs*. 67% in the EBD group) and were substantially higher than in previous retrospective reports for both procedures.[189]

When considering the impact of preoperative biliary drainage on short-term outcomes of surgery, available evidence from meta-analysis of retrospective, non-randomised trials show no differences in 30-day mortality and major postoperative complications. However, long-term outcomes seem more favourable in the EDB group, since risk of seeding metastasis, 5-year recurrence and 5-year survival are worse in the PTBD group. This data needs to be interpreted with caution; indeed, patients included in the PTBD group had more advanced disease, which may have favoured the initial indication to perform a percutaneous over an endoscopic drainage in the first place and may have influenced the long-term prognosis and risk of metastasis after surgery.[190,191] It is interesting to note, however, that a higher incidence of seeding metastasis has also been reported for PTBD in comparison to EBD for dCCA and pancreatic cancer presenting with biliary obstruction.[192]

In patients with eCCA amenable to surgical treatment and an indication for endoscopic biliary drainage, should metallic stent placement be preferred over plastic stent or nasobiliary drainage?

Recommendations

- In dCCA, covered metal stents should be considered first choice in patients where preoperative biliary drainage is indicated **(LoE 1, strong recommendation, strong consensus).**
- In pCCA, no specific stent type can be recommended for preoperative drainage, owing to insufficient evidence, though removable stents are recommended **(LoE 4, weak recommendation, strong consensus).**

The choice of stent for preoperative biliary drainage has been a subject of debate for years, given the lower cost of plastic stents, and that their shorter patency compared to metallic stents may be less of an issue in the preoperative setting. A recent meta-analysis on their comparative performance in periampullary cancers included 440 patients from seven RCTs.[193] In this review, interventions and direct costs were significantly lower with metallic stents, while overall complications did not differ. However, in high-volume centres and in the setting of neoadjuvant chemotherapy, metallic stents also offered benefits. Thus, centre characteristics may impact the choice of stent in the individual patient. Also, the study did not include the role of surgery waiting times which might impact the stent comparison. Finally, it included pancreatic cancers in the group of periampullary cancers, although it is unclear if that matters for this analysis, since studies on pancreatic head cancer have arrived at similar conclusions.[194]

In pCCA, the documentation is sparser as to choice of stents, and no recent data were found. Data from Japan indicate acceptable performance and safety of unilateral plastic nasobiliary drains,[195,196] although a significant incidence of both cholangitis and pancreatitis calls for caution and multidisciplinary discussions. However, in comparison to percutaneous drainage in this setting, transpapillary drainage was recommended.[195] One study on the use of metallic stents *vs.* plastic stents for preoperative drainage favoured metallic stents,[197] but the numbers were small and the study has not been repeated.

In patients with advanced eCCA, what is the preferred modality for drainage?

Recommendations

- In patients with advanced dCCA, the preferred modality for drainage is the endoscopic transpapillary placement of a self-expanding metal stent **(LoE 4, strong recommendation, strong consensus).**
- When adequate expertise is available, endoscopic ultrasound-guided biliary drainage (EUS-BD) should be preferred over PTBD in case of failed ERCP **(LoE 2, strong recommendation, strong consensus).**
- In patients with advanced pCCA, endoscopic transpapillary drainage may be preferred to percutaneous drainage in Bismuth types I and II; percutaneous or combined endoscopic/percutaneous drainage may be preferred in Bismuth types III and IV **(LoE 3, weak recommendation, strong consensus).**
- In patients with advanced pCCA, use of uncovered self-expanding metal stents may be preferred over plastic stent placement **(LoE 3, weak recommendation, strong consensus).**

Adequate biliary drainage is of paramount importance in patients with dCCA and pCCA with advanced disease. The main aims of biliary stenting in such patients are to alleviate or prevent cholangitis, reduce serum bilirubin to levels compatible with the administration of chemotherapy, improve quality of life and possibly OS.[198–200] A careful evaluation of each patient in a multidisciplinary setting is paramount to select the optimal strategy for biliary decompression; planned treatment should also take into consideration the need for multiple interventions, especially with increasing efficacy of medical treatments.

Successful endoscopic decompression of biliary obstruction due to advanced dCCA is usually less technically demanding than in pCCA. Endoscopic transpapillary biliary drainage is therefore mostly recommended as the initial modality for treatment over PTBD. However, studies directly comparing the efficacy and safety of EBD *vs*. PTBD in advanced dCCA are scant. The majority of available data originates from retrospective studies, randomised trials and meta-analyses that all include different aetiologies as the primary causes of extrahepatic obstruction (dCCA, pCCA, pancreatic cancer, gallbladder cancer). In general, the most recent meta-analyses demonstrate a comparable technical success rate and overall complication rate between EBD and PTBD, with lower risk of pancreatitis and cholangitis and higher risk of bleeding and tube dislocation for PTBD.[201–203] Similar short-term mortality rates (30-day) have consistently been demonstrated in meta-analyses, while a recent prospective study showed a significant benefit for internal over external biliary drainage (236.40 ± 33.37 days *vs.* 110.35 ± 26.16 days; p <0.001).[204] Also, quality of life is generally considered superior when endoscopic drainage is performed.[205]

In patients with advanced dCCA, a large body of evidence coming from meta-analyses of randomised trials supports the use of self-expanding metal stents (SEMSs) over plastic stents. SEMSs are associated with a higher therapeutic success rate (OR 0.43), lower 30-day occlusion rate in distal malignant obstruction (OR 0.36) and a lower long-term occlusion rate (OR 0.42) than plastic stents. Also, the risk of complications and re-interventions was lower with SEMSs.[206–208] A survival benefit for SEMSs has been reported in some studies,[207,208] but not in others.[206,209]

With regards to the type of stent (fully covered, partially covered or uncovered) to be used in dCCA, available data are insufficient to formulate a specific recommendation. Primary stent patency, stent dysfunction and complications do not appear to be significantly influenced by the type of stent.[210,211] Despite a recent study reporting a longer time to recurrent biliary obstruction with fully covered SEMSs,[212] this effect seems counterbalanced by higher stent migration and sludge formation rates compared to uncovered SEMSs (OR 5.11 and OR 2.46, respectively).[213] Partially covered SEMSs will also need to be considered in future studies since a recent meta-analysis demonstrated a longer time to recurrent biliary obstruction compared with fully covered SEMSs (369 days *vs.* 238 days).[214] Finally, it is worth mentioning that, contrary to uncovered stents, fully covered SEMSs have the possibility of removal, which facilitates re-interventions in patients with prolonged survival and should be used in all cases where a final diagnosis of malignancy is not yet achieved.

Failure to achieve deep biliary cannulation during ERCP is reported in about 10% of patients with malignant biliary obstruction.[215] In such patients, repeated ERCP or PTBD remain valuable options in clinical practice. In recent years, the use of EUS-BD has emerged as a safe and effective alternative when performed by experienced endoscopists and in referral centres. A number of meta-analyses including randomised

trials have shown that EUS-BD is associated with better clinical success rates, lower adverse event rates, and lower rates of re-intervention (due to decreased risk of stent/catheter dysfunction) compared to PTBD.[216–218] The recent implementation of dedicated one-step stents (*e.g.* electrocautery-enhanced lumen apposing metal stent, Boston Scientific), which were not included in the meta-analysis, is likely to improve the outcome of EUS-BD by facilitating the procedure. In fact, emerging data suggest that EUS-BD may be associated with similar or better clinical success with lower adverse event rates when compared to ERCP as a first-line intervention in distal malignant biliary obstruction.[219,220] It has to be stressed that, even in the expert hands of researchers performing the aforementioned studies, EUS-BD is not devoid of risk, with serious adverse events and in rare cases fatalities reported; thus, it should only be performed by experienced and adequately trained endoscopists.[221,222]

Biliary decompression in patients affected by pCCA is usually more challenging than in dCCA due to the intrinsic complexity of biliary anatomy. Technical complexity of biliary drainage is usually correlated with the extension of proximal biliary invasion according to the Bismuth-Corlette classification. At present, studies that specifically evaluated the best drainage modality for advanced unresectable pCCA are limited, retrospective in nature and heterogenous.[223–226] In general, these studies showed no significant difference between endoscopic or percutaneous drainage in terms of success of drainage and mean survival time,[223,224,227] with single reports either favouring the percutaneous[225] or the endoscopic approach.[226] RCTs comparing endoscopic *vs*. percutaneous biliary drainage yielded conflicting results and were only performed in patients with resectable pCCA,[189] perihilar obstruction due to gallbladder cancer,[228] and in biliary obstruction of different causes and endoscopically treated with plastic stents.[229] A meta-analysis evaluating only patients affected by type III and IV pCCA according to the Bismuth-Corlette classification showed higher odds of successful biliary drainage for PTBD *vs.* EBD (OR 2.53; 95% CI 1.57-4.08), with a tendency towards lower overall adverse event rates (OR 0.81; 95% CI 0.52-1.26) and 30-day mortality (OR 0.84; 95% CI 0.37-1.91).[230] These results were confirmed in a more recent meta-analysis demonstrating higher clinical success rates and a lower incidence of cholangitis in the PTBD group of patients with advanced pCCA.[188]

In the setting of advanced pCCA, data originating from previous RCTs have shown superior outcomes for SEMSs in terms of successful drainage rate and survival,[231] number of re-interventions and hospitalisations for stent dysfunction,[232] and 6-month patency rate.[233] Not surprisingly, available meta-analyses that include these trials have shown similar results.[207,234] However, these data need to be interpreted with caution. The definition of stent patency is heterogeneous in the literature (*e.g.* definition of stent occlusion, stent occlusion *vs.* migration), and this may have biased the results of meta-analyses on this aspect.[235] Moreover, more recent retrospective data suggests that plastic stents may be associated with lower stent-related side effects,[236] and that the number of repeated ERCP may be comparable when only non-elective re-interventions are included in the evaluation.[237] Finally, it has to be mentioned that intraductal radiofrequency ablation is being actively investigated in order to prolong survival and stent patency;[238,239] while this technique is feasible with plastic stents, its efficacy remains to be determined in patients treated with SEMSs.

In patients with advanced eCCA, do endoscopic ablative techniques (i.e. radiofrequency ablation, photodynamic therapy, brachytherapy) improve survival and/or stent patency?

Recommendation

- In dCCA, intraductal radiofrequency ablation is currently not standard of care; however, it may be considered in combination with stent therapy to improve stent patency. Data on survival benefit are inconclusive **(LoE 2, weak recommendation, strong consensus).**

Intraductal ablative techniques have been variably attempted for improvement of stent patency and survival in malignant biliary obstruction. Photodynamic therapy was initially deemed promising, but initial optimism was mitigated by the impracticality of the method as well as the development of alternatives. During recent years, radiofrequency ablation has been developed, following the initial report by Steel *et al.*.[240] A meta-analysis of six RCTs including 439 patients with malignant biliary obstruction concluded that radiofrequency ablation + stent placement was associated with a moderate survival benefit of 85 days *vs*. stent placement alone.[238] The analysis included both metallic and plastic stents, and a combination of pCCA and dCCA. In subgroup analyses, the survival benefit was restricted to the extrahepatic lesions, while improved stent patency was also shown for pCCA. No increase in adverse events was seen, despite initial concerns about hepatic artery injury with haemobilia. In a meta-analysis including five randomised trials and 370 patients with inoperable eCCA, OS was not different in patients treated with radiofrequency ablation; however, subgroup analysis showed a trend towards improved survival in studies employing plastic stents in the radiofrequency ablation-treated group (HR 0.42; 95% CI 0.22-0.80; $p = 0.009$; $I^2 = 72\%$).[239]

In terms of other local ablative techniques, catheter-based brachytherapy[241] as well as chemotherapy by drug-eluting stents[242] has been attempted, but so far these techniques remain mainly investigational or experimental.

Follow-up

In patients who have undergone curative-intent surgery for eCCA, which follow-up biochemistry and imaging tests should be performed and at what intervals to detect recurrence early?

Recommendation

- Contrast-enhanced thorax-abdomen-pelvis CT or contrast-enhanced abdominal MRI with thorax CT and tumour marker tests (CA19-9 and carcinoembryogenic antigen [CEA] with or without cancer antigen 125 [CA125]) should be performed after surgery, every 3-4 months in year 1, every 6 months in year 2, and annually thereafter until 5 years from surgery **(LoE 4, strong recommendation, consensus).**

It is unclear whether performing post-operative and post-adjuvant treatment follow-up for patients who have undergone treatment with curative intent for eCCA impacts survival. However, current practice probably favours such follow-up assuming that early identification of recurrence may allow for early initiation of therapy.

When performing biochemistry and imaging follow-up after curative treatment, the tumour marker of choice is CA19-9.[73] Performing additional CEA and CA125 testing is supported by the prognostic impact that these markers have also shown in the setting of early and advanced disease.[139,243] In terms of imaging, thoracoabdominal CE-CT seems the best approach.

The optimal frequency of such investigations has not been tested in prospective studies. The most reliable source of influence for clinical practice is probably the BilCap clinical trial,[165] which established capecitabine as the current standard therapy in this setting and in which biochemistry and imaging follow-up was performed every 3 months in year 1, every 6 months in year 2, and annually thereafter until completion of 5 years of follow-up. After 5 years of follow-up and in the absence of recurrence, patients could be offered the opportunity to stop follow-up.

In patients receiving systemic palliative treatment for eCCA, which follow-up biochemistry and imaging tests should be performed to assess response?

Recommendation

- Contrast-enhanced thorax-abdomen-pelvis CT or contrast-enhanced abdominal MRI with thorax CT and tumour marker tests (CA19-9, CEA with or without CA125) should be performed every 3 months to assess response to systemic and locoregional palliative treatments **(LoE 4, strong recommendation, strong consensus).**

For patients diagnosed with advanced eCCA who are receiving any form of palliative therapy, it is important to assess benefit or lack of benefit from such therapy. Despite the absence of studies specifically exploring the most suitable follow-up intervals in this setting, and acknowledging that many of the clinical trials exploring new treatment options in eCCA perform reassessment of response every 8 weeks (especially when PFS is one of the main end-points), within clinical practice and outside the setting of clinical trials, it is widely accepted to perform biochemistry and imaging every 3 months. Thoracoabdominal CE-CT may be enough unless it does not allow for adequate imaging of the site of disease in one specific individual, in which case MRI may be considered. The role of FDG-PET in this setting is unclear and it is not widely recommended.[109] In terms of tumour markers, CA19-9 is the most widely employed.[244] However, it was shown that the combination of CA19-9, CEA and CA125 had prognostic value and, if possible, testing the three of them should be considered.[139]

Conclusions and future directions

In recent years, significant advances in imaging, molecular profiling, and systemic therapies have consistently entered clinical practice. Despite these strides, challenges persist in early detection, precise classification, and management due to the anatomical complexity and heterogeneous nature of these tumours. Future efforts should focus on refining molecular and genetic profiling to better distinguish CCA subtypes and identify actionable targets, expanding clinical trials for novel therapeutic combinations, and implementing more effective surveillance strategies for high-risk populations. The integration of liquid biopsy technologies and bile-based molecular analyses holds promise for improving diagnostic accuracy and personalising treatment. Moreover, biliary drainage approaches should focus on decreasing the high risk of complications and getting more patients to treatment. Collaborative international efforts are essential to standardise staging systems, enhance therapeutic outcomes, and ensure equitable access to emerging technologies, paving the way for the more individualised and effective management of CCA.

Appendix. Delphi round agreement on the recommendations of the present clinical practice guidelines.

Recommendation	Consensus
The term extrahepatic cholangiocarcinoma/eCCA should indicate malignancies arising from hepatic ducts (right, left and common) and the bile duct (frequently referred to as the common bile duct or ductus choledochus). The term "biliary tract cancer" should be used as a wide definition comprising all malignant neoplasms arising from the biliary tree, including intrahepatic CCA, extrahepatic CCAs, and gallbladder and ampullary carcinoma with biliary differentiation **(LoE 5, strong recommendation).**	96%
Given the significant differences in pathobiology, clinical presentation and management, the sub-classification and recording of CCA should be tripartite (iCCA *vs.* pCCA *vs.* dCCA) **(LoE 5, strong recommendation).**	96%
Genetic alterations cannot currently be used to distinguish iCCA from perihilar/distal eCCA **(LoE 5, weak recommendation).**	88%
Data should be routinely recorded for CCA cases, noting whether they have recognised risk factors, specifying those risk factors, or if no known risk factors are present **(LoE 5, strong recommendation).**	100%
Germline mutations testing and genetic counselling cannot currently be recommended for all patients with a diagnosis of pCCA and dCCA **(LoE 4, weak recommendation).**	83%
Patients with pCCA/dCCA and a personal and/or familial cancer history suggestive of hereditary cancer syndromes or with pCCA/dCCA with microsatellite instability or genetic alterations potentially linked with hereditary syndromes should receive genetic counselling with germline mutations testing as appropriate **(LoE 5, strong recommendation).**	100%
In patients with PSC, regular surveillance should be performed to detect development of malignancy **(LoE 3, strong recommendation).**	96%
Patients with choledochal cysts should be operated on and subsequently undergo surveillance **(LoE 3, strong recommendation).**	91%
Patients with liver flukes should be treated, but a specific surveillance programme cannot currently be recommended owing to insufficient evidence **(LoE 4, weak recommendation).**	100%
Patients with PSC should undergo annual ultrasound and/or MRI surveillance, with or without CA19-9 testing, with modifications according to relevant risk factors **(LoE 3, strong recommendation).**	82%
Patients with choledochal cysts and liver flukes may be followed after resection/treatment, with minimally invasive tests (biochemistry and ultrasound) **(LoE 4, weak recommendation).**	96%
Contrast-enhanced CT and contrast-enhanced MRI should be used for the diagnosis of pCCA or dCCA as they are superior to ultrasound **(LoE 4, strong recommendation).**	100%
Contrast-enhanced MRI with magnetic resonance cholangiopancreatography (MRCP) should be used to accurately assess the level and extent of the biliary obstruction as it is superior to contrast-enhanced CT (**LoE 3, strong recommendation).**	96%
The use of CA19-9 serum levels to support the diagnosis of eCCAs is not recommended **(LoE 2, strong recommendation).**	85%
CA19-9 serum levels can be used as a prognostic biomarker for overall survival in pCCA and dCCA **(LoE 4, weak recommendation).**	96%
It is suggested that all reasonable attempts be made to obtain an unequivocal histological or cytological diagnosis **(LoE 5, open recommendation).**	93%
When cytological and histological analyses are equivocal and inconclusive but there is a strong clinical suspicion, it is suggested to proceed with stage appropriate surgical treatment in potentially resectable lesions after a full discussion with the multidisciplinary team and the patient; chemotherapy or radiotherapy usually require the demonstration of tumoural tissue **(LoE 5, open recommendation).**	100%
ERCP with brush cytology and, whenever possible, ERCP-guided endobiliary forceps biopsy is suggested as the primary tool for acquiring tissue in cases of suspected eCCA **(LoE 4, weak recommendation).**	89%
ERCP with cholangioscopy-directed biopsies is suggested when: i) previous ERCP sampling in suspicious lesions was negative and ii) competence in cholangioscopy is available in the centre or in an accessible referral hospital **(LoE 4, weak recommendation).**	96%
Liquid biopsies from bile or plasma are interesting future modalities for CCA detection but cannot currently be recommended beyond research and clinical trial settings **(LoE 4, open recommendation).**	93%
Staging should be performed before any biliary stent placement. Multiphasic contrast-enhanced thorax-abdomen-pelvis CT should be used to assess hepatic artery and portal vein involvement and to look for distant metastases **(LoE 3, strong recommendation).**	96%
Contrast MRI with MRCP should be used to analyse bile duct anatomy and the longitudinal extent of the tumour **(LoE 4, strong recommendation).**	96%
In the setting of possible surgical treatment, EUS-guided fine need aspiration/biopsy of lymph nodes should be performed to rule out metastatic lymph nodes **(LoE 4, strong recommendation).**	83%
^{18}F-fluorodeoxyglucose positron-emission tomography (FDG-PET) should not be used for the diagnosis and local staging of eCCA **(LoE 3, strong recommendation).**	100%
For patients with pCCA, the current American Joint Committee on Cancer (AJCC) TNM staging system is suggested **(LoE 4, open recommendation).**	100%
Patients with localised pCCA should be treated with surgical resection if a complete resection (*i.e.* R0) is feasible with acceptable postoperative mortality **(LoE 2, strong recommendation).**	96%
In patients with node-positive pCCA (N1), surgical resection can only be recommended if positivity is limited to perihilar lymph nodes and the anticipated postoperative mortality is acceptable **(LoE 3, weak recommendation).**	96%
Selected patients with (a suspicion of) pCCA may undergo portal vein or arterial reconstruction if required to achieve R0 resection **(LoE 3, weak recommendation).**	100%
Neoadjuvant chemoradiotherapy followed by LT can be considered for selected patients with early-stage (T1-2 which are less than 3 cm, N0, M0) unresectable pCCA **(LoE 3, weak recommendation).**	96%
Gemcitabine and cisplatin in combination with either durvalumab or pembrolizumab should be considered standard of care for the first-line systemic treatment of patients with unresectable or metastatic eCCA **(LoE 2, strong recommendation).**	93%
In the absence of targetable alterations, FOLFOX should be offered as a subsequent line of systemic therapy for patients diagnosed with advanced eCCA who have tumour progression on first-line therapy. Alternatives to consider include irinotecan-based options (based on phase II trial data) **(LoE 2, strong recommendation).**	93%
Patients with unresectable or metastatic eCCA should receive molecular profiling to identify and therapeutically address actionable alterations and to support inclusion into clinical trials **(LoE 2, strong recommendation).**	96%
Adjuvant capecitabine should be offered to patients with resected invasive (excluding tumour *in situ*) eCCA regardless of T, N and resection margin status **(LoE 2, strong recommendation).**	85%

(*continued on next page*)

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Recommendation	Consensus
Chemoradiotherapy cannot be recommended routinely after R0/R1 resection of eCCA, but it may be considered in individual patients with eCCA, especially in an R1 situation **(LoE 3, weak recommendation).**	93%
In patients with eCCA amenable to surgical treatment, routine preoperative biliary drainage should be avoided **(LoE 1, strong recommendation).**	85%
Preoperative drainage should be considered in case of cholangitis, renal failure, intractable pruritus, high bilirubin values, neoadjuvant chemotherapy, planned extensive surgery or expected long waiting time for surgery **(LoE 3, strong recommendation).**	100%
In patients with dCCA amenable to surgical treatment with an indication for biliary decompression, endoscopic drainage should be preferred over percutaneous drainage **(LoE 3, strong recommendation).**	96%
In patients with pCCA amenable to surgical treatment with an indication for biliary decompression, endoscopic drainage cannot be recommended over percutaneous drainage owing to insufficient evidence **(LoE 3, weak recommendation).**	80%
In dCCA, covered metal stents should be considered first choice in patients where preoperative biliary drainage is indicated **(LoE 1, strong recommendation).**	100%
In pCCA, no specific stent type can be recommended for preoperative drainage, owing to insufficient evidence, though removable stents are recommended **(LoE 4, weak recommendation).**	96%
In patients with advanced dCCA, the preferred modality for drainage is the endoscopic transpapillary placement of a self-expanding metal stent **(LoE 4, strong recommendation).**	96%
When adequate expertise is available, endoscopic ultrasound-guided biliary drainage (EUS-BD) should be preferred over PTBD in case of failed ERCP **(LoE 2, strong recommendation).**	100%
In patients with advanced pCCA, endoscopic transpapillary drainage may be preferred to percutaneous drainage in Bismuth types I and II; percutaneous or combined endoscopic/percutaneous drainage may be preferred in Bismuth types III and IV **(LoE 3, weak recommendation).**	100%
In patients with advanced pCCA, use of uncovered self-expanding metal stents may be preferred over plastic stent placement **(LoE 3, weak recommendation).**	96%
In dCCA, intraductal radiofrequency ablation is currently not standard of care; however, it may be considered in combination with stent therapy to improve stent patency. Data on survival benefit are inconclusive **(LoE 2, weak recommendation).**	83%
Contrast-enhanced thorax-abdomen-pelvis CT or contrast-enhanced abdominal MRI with thorax CT and tumour marker tests (CA19-9 and carcinoembryogenic antigen [CEA] with or without cancer antigen 125 [CA125]) should be performed after surgery, every 3-4 months in year 1, every 6 months in year 2, and annually thereafter until 5 years from surgery **(LoE 4, strong recommendation, strong consensus).**	89%
Contrast-enhanced thorax-abdomen-pelvis CT or contrast-enhanced abdominal MRI with thorax CT and tumour marker tests (CA19-9, CEA with or without CA125) should be performed every 3 months to assess response to systemic and locoregional palliative treatments **(LoE 4, strong recommendation**	96%

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Abbreviations

AJCC, American Joint Committee on Cancer; ASC, active symptom control; CA125, cancer antigen 125; CA19-9, carbohydrate antigen 19-9; CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; CPGs, clinical practice guidelines; dCCA, distal CCA; EASL, European Association for the Study of the Liver; EBD, endoscopic biliary drainage; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; EUS-BD, EUS-guided biliary drainage; EUS-TA, EUS-guided tissue acquisition; EV, extracellular vesicles; FDG-PET, ^{18}F-fluorodeoxyglucose positron-emission tomography; HR, hazard ratio; LT, liver transplantation; MRCP, magnetic resonance cholangiopancreatography; OR, odds ratio; pCCA, perihilar CCA; PFS, progression-free survival; PSC, primary sclerosing cholangitis; PTBD, percutaneous transhepatic biliary drainage; RCT, randomised-controlled trials; SEMSs, self-expanding metal stents; WHO, World Health Organisation.

Conflict of interest

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Supplementary data

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