Biliary tract cancers: French national clinical practice guidelines for diagnosis, treatments and follow-up (TNCD, SNFGE, FFCD, UNICANCER, GERCOR, SFCD, SFED, AFEF, SFRO, SFP, SFR, ACABi, ACHBPT)☆

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ABSTRACT

Introduction: This document is a summary of the French intergroup guidelines of the management of biliary tract cancers (BTC) (intrahepatic, perihilar and distal cholangiocarcinomas, and gallbladder carcinomas) published in September 2023, available on the website of the French Society of Gastroenterology (SNFGE) (www.tncd.org).

Methods: This collaborative work was conducted under the auspices of French medical and surgical societies involved in the management of BTC. Recommendations were graded in three categories (A, B and C) according to the level of scientific evidence until August 2023.

Results: BTC diagnosis and staging is mainly based on enhanced computed tomography, magnetic resonance imaging and (endoscopic) ultrasound-guided biopsy. Treatment strategy depends on BTC subtype and disease stage. Surgery followed by adjuvant capecitabine is recommended for localised disease. No neoadjuvant treatment is validated to date. Cisplatin-gemcitabine chemotherapy combined to the anti-PD-L1 inhibitor durvalumab is the first-line standard of care for advanced disease. Early systematic tumour molecular profiling is recommended to screen for actionable alterations (*IDH1* mutations, *FGFR2* rearrangements, *HER2* amplification, *BRAF*[V600E] mutation, MSI/dMMR status, etc.) and guide subsequent lines of treatment. In the absence of actionable alterations, FOLFOX chemotherapy is the only second-line standard-of-care. No third-line chemotherapy standard is validated to date.

Conclusion: These guidelines are intended to provide a personalised therapeutic strategy for daily clinical practice. Each individual BTC case should be discussed by a multidisciplinary team.

1. Introduction

1.1. Methodology

The present article is a summary of the French intergroup guidelines published in September 2023 (http://www.tncd.org). These guidelines are a collaborative work written by a multidisciplinary committee (Thésaurus National de Cancérologie Digestive, TNCD) originating from 12 medical and surgical societies (SNFGE, FFCD, UNICANCER, GERCOR, SFCD, SFED, AFEF, SFRO, SFP, SFR, ACABi, ACHBPT) comprising experts from different specialties involved in the management of biliary tract cancers (BTCs) (oncologists, gastroenterologists, surgeons, pathologists, radiation oncologists and radiologists). These guidelines do not address ampullary carcinomas and combined hepato-cholangiocarcinomas, which are dealt with in dedicated chapters. The work is based on the extraction from the Medline database in August 2023 for randomised trials, meta-analyses, consensus conferences and recommendations for clinical practice with the keywords "biliary tract cancer", "gallbladder carcinoma" and "cholangiocarcinoma", in English or French, without date limitation.

Recommendations were graded according to the level of scientific evidence (from 'high' [e.g. several randomised controlled trials/meta-analysis] to 'very low' [expert opinion (agreement or not)]) following the French Health Authority guidelines (www.has-sante.fr) and scored according to the GRADE system (from A to D) (Table 1).

The document was reviewed and modified after further evaluation by a review committee followed by a final validation from the TNCD steering committee.

1.2. Epidemiology

BTCs include gallbladder carcinoma (GBC), cholangiocarcinoma (CCA) and ampullary adenocarcinoma. BTCs are uncommon cancers,

Table 1
Grade of recommendations.

Grade	Quality of evidence	Definition
A	High	Strongly recommended based on highly robust scientific evidence (e.g. several randomised controlled trials/meta-analysis). Further research is very unlikely to change our confidence in the estimate of effect.
B	Moderate	Usually recommended based on scientific presumption (e.g. one randomised controlled trial). Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C	Low	Option based on weak scientific evidence (e.g. one or several non-randomised trials). Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
D	Very low	Expert opinion (agreement or not). Any estimate of effect is very uncertain.

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with a worldwide estimated incidence of 2.1 in men and 2.4 in women per 100,000 person-years in 2018. Highest incidence areas are reported in Southeast Asia for CCA, and Northern India and Western South America for GBC [1,2]. In France, incidence was 2.1 in men (increase of 1.1%/year over the period 1990–2018) and 1.4 in women (decrease of 1.2%/year) in 2018, with incidence rates rising sharply from age 50 (median age at diagnosis, 72 years in men and 78 years in women) [3]. BTCs account for 2% of digestive cancers and 10–15% of primary liver cancers [4–6]. The main risk factors are cholelithiasis, biliary distomatoses (liver flukes) in Asia, chronic inflammatory diseases of bile ducts, metabolic syndrome with non-alcoholic steatohepatitis (NASH), tobacco consumption, hepatitis B and C virus chronic infections (relative risk: 5) and liver cirrhosis (relative risk: 20). In France as in other Western countries, the rise in incidence of intrahepatic cholangiocarcinoma (iCCA) – whereas the incidence of extrahepatic cholangiocarcinoma is stable – is likely mostly due to the increase of liver chronic diseases [7,8]. BTCs have a poor prognosis, which did not substantially improve over the past 30 years. In France, relative survival rates at 1, 3 and 5 years after diagnosis (all stages) were estimated at 25%, 10% and 7%, respectively [5]. A recent analysis from the French nationwide database of the 3650 patients with iCCA hospitalised in 2014 and 2015 in France showed that 65% of patients received only best supportive care at diagnosis [9].

2. Diagnosis and staging

2.1. Classification

The TNM-AJCC-UICC classification splits BTCs according to their location (Figures 1), into 1) CCA, subdivided in iCCA (10–20%), developed from second-order intrahepatic bile ducts, perihilar CCA (pCCA) (50%), developed from the right, left and/or common hepatic duct, and distal CCA (dCCA) (30–40%), developed from the common bile duct downstream the insertion of the cystic duct; 2) GBC; 3) ampullary adenocarcinoma [10]. TNM classifications and prognostic stages are detailed in Supplementary Tables 1 and 2.

The Bismuth-Corlette classification, based on the proximal level of

tumour biliary extension, is used to assess the resectability of pCCA (Figure 1) [9]. However, it does not take into account vascular involvement, leading to underestimation of tumour invasion in 30% of cases. The XY classification distinguishes type X from type Y pCCA according to invasion or not of the confluence between left lateral ducts (B2 and B3) [11]. Type Y pCCAs are often resectable through extended right-sided hepatectomy, while type X is frequently associated with arterial invasion requiring complex vascular reconstructions (Figure 1).

2.2. Diagnosis and pre-treatment workup

While at early stages, diagnosis is often incidental, at advanced stages, the clinical presentation may include general health status deterioration, jaundice (especially for pCCA and dCCA), abdominal pain and hepatomegaly [12–14]. Recommended examinations at baseline, their indications and objectives are summarized in Table 2.

2.2.1. Imaging

Imaging is essential for diagnosis, staging and treatment decision. It determines the level of bile duct obstruction and the level of invasion of the liver, vessels, lymph nodes and distant sites.

Baseline explorations should include contrast-enhanced thoraco-abdomino-pelvic computed tomography (CT) for positive diagnosis and staging [15], contrast-enhanced liver magnetic resonance imaging (MRI) in iCCA, and cholangio-MRI in pCCA/dCCA. CT and MRI should be performed before any biliary stent placement to optimally assess biliary extension [16,17]. Depending on the context, 18 F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) for detection of potential extrahepatic lesions, and endoscopic ultrasonography (EUS) for locoregional staging and tissue sampling may be considered [18,19].

2.2.2. Pathological diagnosis

Percutaneous biopsy of both tumour tissue and non-tumour liver tissue is recommended in iCCA for positive diagnosis, molecular profiling, and assessment of an underlying chronic liver disease [20]. In pCCA/dCCA, samples are usually obtained through bile duct brushing,
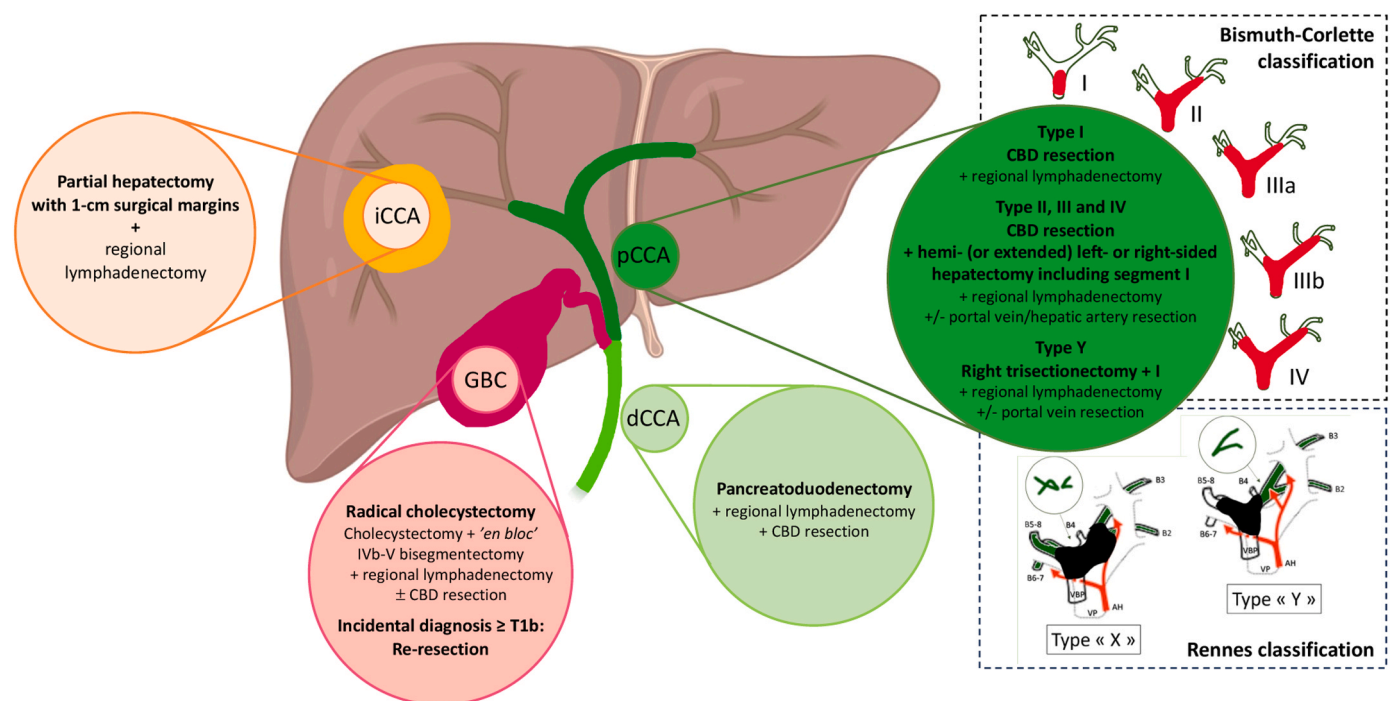

Fig. 1. Classifications and surgical management. Abbreviations: CBD, common biliary duct; dCCA, distal cholangiocarcinoma; GBC, gallbladder carcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma.

Table 2
Biliary tract cancers: diagnostic and pretherapeutic work-up.

Examinations	Indications and Objectives
CT	TAP CT: first intention examination; should be performed before any endobiliary procedure. Liver volumetry prior to major hepatectomy.
Liver MR imaging	Should be performed in the absence of extrahepatic metastases to explore resectability before any endobiliary procedure. Resectable iCCA: should include diffusion and gadolinium-enhanced sequences.
MR cholangiography	pCCA and dCCA: should be performed before any endobiliary procedure
Liver biopsy	iCCA: • Biopsy of tumor and non-tumor liver parenchyma to search for underlying liver disease • If histology unconclusive, IHC study with CK7, CK20, CDX2/SATB2, TTF1, GATA3 (female); CRP as 2nd-line test pCCA: not recommended in the absence of metastasis.
ERCP	pCCA and dCCA: not recommended if biliary drainage not necessary. If performed: • Combine biliary brushing (with thin-layer cytology) and endobiliary biopsies (cytobloc technique ideally) • If samples are negative or atypical: rapid cytological review by expert pathologist • If diagnosis remains uncertain: 2nd ERCP in a specialised center with brushing, biopsies and cholangioscopy
Endoscopic ultrasonography	pCCA and dCCA 1. Resectable/transplantable tumor in an operable patient: • FNA/FNB of the primary tumor must be discussed with an expert hepatobiliary surgeon due to the theoretical risk of tumor dissemination • FNA/FNB of any suspicious lymph node 1. Unresectable/untransplantable tumour or inoperable patient: FNA/FNB of the primary tumour or suspicious lymph node(s) possible.
Cholangioscopy	Not recommended as 1st-intention procedure
GI tract endoscopies	May be considered for differential diagnosis (iCCA).
FDG-PET	Not routinely recommended for extension work-up. May be considered for differential diagnosis.
IgG4 (serum assay, IHC)	May be considered for differential diagnosis (pCCA and dCCA)
Biological liver tests	Liver function evaluation (prothrombin time, albumin, bilirubin, etc) recommended, especially in iCCA
Laparoscopy	To be discussed if resection is envisaged (without delaying it), particularly if high risk of non-resectability

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; FDG PET, fluorodeoxyglucose positron emission tomography; FNA, fine-needle aspiration; FNB, fine-needle biopsy; GI, gastrointestinal; IHC, immunohisto-chemistry; Ig, immunoglobulin; LT, liver transplantation; MR, magnetic resonance; TAP CT, thoraco-abdomino-pelvic computed tomography.

biopsies or bile aspiration during endoscopic retrograde cholangiography (ERC) when biliary drainage is needed, with sensitivities varying from 40% to 84%, or through fine needle aspiration during EUS [21–24]. After one or more ERC with negative samples, cholangioscopy should be considered, as well as IgG4 plasma level determination, especially in cases of indeterminate biliary strictures as cholangioscopy enables direct visualization of the biliary epithelium and targeted biopsies [25,26] with higher sensitivity than ERC-guided brushing (68.2% vs. 21.4%, p < 0.01) [27]. As up to 10–15% of resected pCCA strictures are eventually non-cancerous on pathological examination, pathological confirmation is essential before any treatment [28,29]; however, additional procedures should not delay treatment. Thus, if clinical and radiological presentation is typical, but cytopathological examination is only suspicious for cancer or remains negative after two attempts, surgery or palliative-intent treatment may be initiated after validation by a specialized multidisciplinary team (expert agreement). Molecular

techniques (e.g., high-throughput sequencing [NGS], in situ hybridisation [ISH]) should be considered to improve chances of diagnosis (grade B).

2.2.3. Serum biomarkers

There are no circulating tumour markers specific to BTCs. Carbohydrate antigen (CA) 19.9 has a sensitivity and specificity of around 80% (studied mainly in primary sclerosing cholangitis) [30]. Carcinoembryonic antigen (CEA) and CA125 are less sensitive (30–50%) and no more specific [31]. All three markers may be elevated in benign biliary obstructions. Persistent elevation after effective biliary drainage is suggestive of cancer.

2.2.4. Differential diagnosis

The main differential diagnoses for iCCA are metastases from adenocarcinoma of another origin, hepatocellular carcinoma and hepatocholangiocarcinoma. In case of doubt with liver metastases from a carcinoma of unknown primary or from a non-biliary origin, tumour immunohistochemistry (IHC) may be helpful for the diagnosis of CCA, which is typically cytokeratin (CK)7 + , CK19 + , CK20 + /-. Colorectal adenocarcinoma metastases are often easily identifiable on standard morphology and on their immunophenotype, which is predominantly CK7-, CK20 + , CDX2 + and SATB2 + . On the other hand, differential diagnosis with metastases of pancreatic, gastric or extrahepatic biliary origin can be difficult, requiring the conjunction of several immuno-histochemical markers (Figure 2). Other markers may help to better characterize tumour origin such as GATA3 (breast cancer), TTF1 (lung cancer), CDX2 (gastro-entero-colic differentiation marker) or HepPar1, glypican-3, Argininase-1 and AFP (hepatocytes and HCC markers). C-reactive protein (CRP) IHC, already used for the diagnosis of inflammatory hepatocellular adenomas, appears promising for differentiating iCCA (particularly of the "small-duct" type) from liver metastases of pancreatic and gastric adenocarcinoma. Its performance is better than that of N-cadherin with a sensitivity and specificity on surgical samples of 93.3% and 88.2%, respectively, versus 80.0% and 88.2% respectively for N-cadherin [32]. However, when possible, extensive IHC exploration should be avoided to preserve tissue samples for tumour molecular profiling. Additional investigations (e.g., mammography, PET, digestive tract endoscopies) may also be considered without delaying treatment's initiation.

2.2.5. Detection of familial predisposition

Hereditary forms of BTCs have been reported with germline mutations in *BRCA* genes or mismatch repair deficiency (MMR) genes (Lynch syndrome). In a large cohort of 1292 patients with BTC, BRCA mutations were detected in 3.6% (n = 46) of samples (BRCA1: 0.6%, BRCA2: 3%) and microsatellite instability (MSI)-high/ deficient(d)MMR in 2.4% of tumours [33]. Exceptional family aggregations of BTCs of unknown genetic substratum have also been reported [34]. No systematic germline screening for BTCs is recommended in France and worldwide.

3. Management of local/locoregional disease

Therapeutic recommendations and options according to BTC subtype and stage with levels of evidence are presented in Figure 3 and Table 3.

3.1. Neoadjuvant setting

In the absence of randomised trial to date, neoadjuvant therapy should be restricted to the context of clinical trials. If an initially unre-sectable iCCA responds to systemic and/or locoregional therapy, surgery should be discussed again by a multidisciplinary team [35,36].

3.2. Surgery

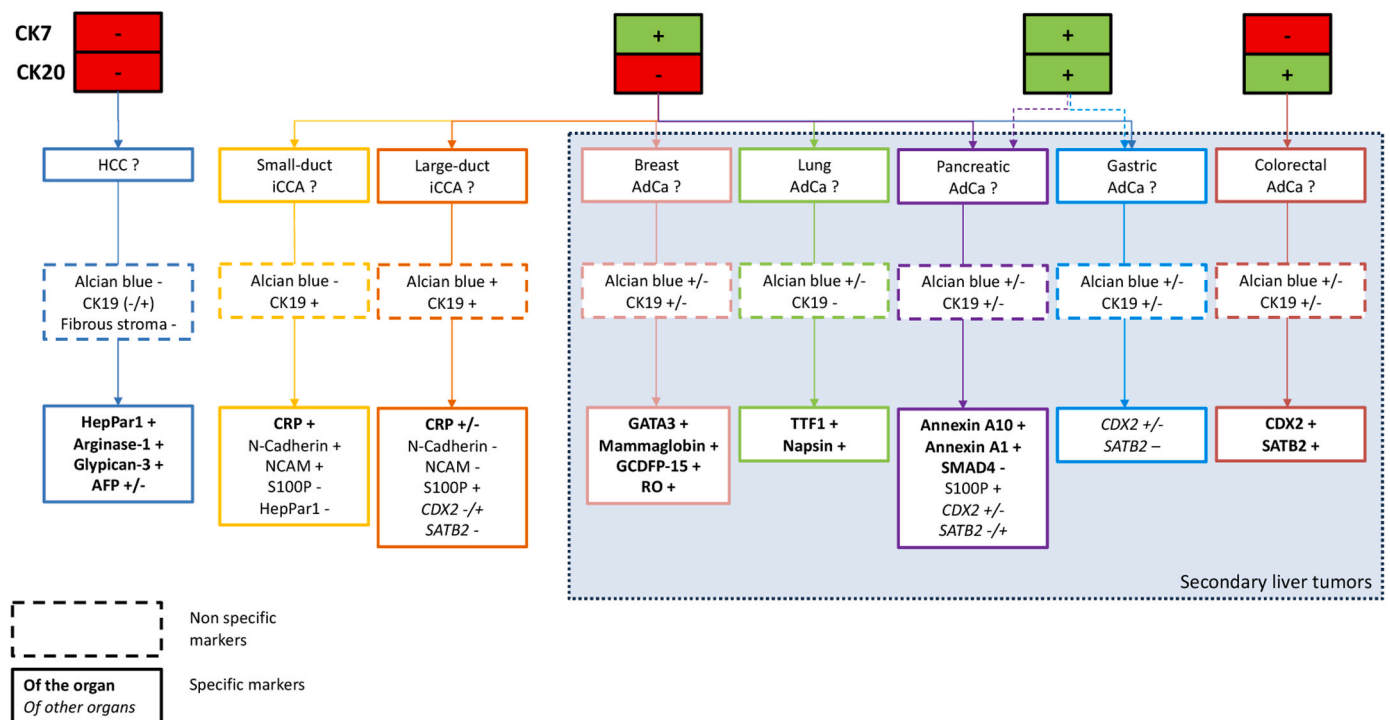Surgery objectives include complete surgical resection (R0 margin

Fig. 2. Intrahepatic adenocarcinoma: Immunohistochemistry analyses algorithm to determine the tumor origin. Unusual profiles are possible, particularly on biopsy, for example: iCCA: CK7- (<5%), CK19- (<10%), GATA3 + (5%), HepPar1 + /GLY-3 + (<10%), or even AFP+ ; HCC: CK7 + , CK19 + (5–20%), CK20 + (<5%), HepPar1 or GLY-3 or arginase-, depending on differentiation and subtype. Abbreviations: AdCa, adenocarcinoma; AFP, alpha-fetoprotein; CK, cytokeratin; CRP, C-reactive protein; GCDFP15, gross cystic disease fluid protein 15; GLY-3: glypican-3; HCC, hepatocellular hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma; OR, oestrogen receptors.

status) while preserving an adequate remaining liver volume. However, even after R0 resection, 5-year overall survival (OS) does not exceed 5–10% in GBC, except for early stages (Tis-T1a) (5-year OS, 95–100%) [37], and 12–40% in CCA [38–40]. Recommended surgical techniques according to BTC anatomical subtypes are summarized in Figure 1.

A standardized pathology report must be drawn up, depicting at least tumour type, associated (pre)neoplastic lesions, differentiation grade, stage, surgical margin status, lymphatic, vascular, perineural and lymph node invasion, and distant metastases.

Main poor prognostic factors are lymph node invasion, macro-vascular invasion and microscopic invasion of the resection margins (R1). Since up to 65% of patients eligible to curative-intent surgery ultimately have metastatic or unresectable disease, local resectability assessment, and peritoneal cavity exploration by preoperative laparoscopy [41] are essential, as well as intraoperative frozen sections examination of the biliary margin(s) in pCCA, dCCA and GBC. 1-cm safety margins are advocated for iCCA, even though the level of evidence is low, since the prognosis for resection with < 5 mm margins is close to that of R1 tumours [42]. Systematic locoregional lymphadenectomy (of ≥6 nodes in iCCA and >5 nodes in other BTCs) is recommended due to its major prognostic impact [43–46]. Lymphatic invasion beyond the first lymph node relay contraindicates resection; however, the sole suspicion of lymph node involvement on preoperative imaging should not contraindicate surgery due to the high false positive rate [47–49].

In most jaundiced patients with pCCA, preoperative biliary stenting is necessary. Before a left- or right-sided hepatectomy, the choice of the liver segments to be stented should be discussed with the surgical team beforehand, as the biliary clearance of the future liver remnant would be necessary and sufficient in most cases. Preoperative management should articulate biliary stenting and portal vein embolization, as necessary.

Bismuth type I pCCA requires resection of the common bile duct with regional lymphadenectomy. The benefit of extending lymphadenectomy to retro-pancreatic region has not been demonstrated. Bismuth type II,

III or IV pCCAs require an extended (right or left-sided) hepatectomy, combined with vascular resection if needed [50]. Associated vascular resections in case of tumour extension to portal vein and/or hepatic artery have been proved to safely extend resectability rates in selected patients [51]. Longitudinal biliary extension, unilateral vascular invasion and subsequent liver atrophy guide the choice of the type of surgery. Segment I resection is recommended for Bismuth type II or higher pCCA, since bile ducts directly originating from the upper limit of the hilar plate are invaded in approximately 90% of the cases. Right tri-segmentectomy extended to segment I is recommended if the tumour spares the B2-B3 convergence (type Y), as the left hepatic duct is longer and the right hepatic artery is often invaded [11].

dCCA requires pancreatoduodenectomy with standard lymphadenectomy and resection of the common bile duct [52].

>T1a GBC requires radical cholecystectomy, which consists in en-bloc resection of gallbladder and adjacent liver parenchyma (segments IVb + V) and regional lymphadenectomy, plus common bile duct resection in case of biliary extension beyond the cystic duct. The rate of lymph node invasion increases with stage (Tis, 0%; T1a, 2–5%; T1b, 15–20%; T2, 9–30%; T3, 39–72% and T4, 67–80%) [53–58]. In case of lymph node invasion, 5-year OS rate is very low to null [59,60]. Lymphadenectomy includes at least extensive dissection of hepatic pedicle nodes, but may be extended to anterior and posterior pancreatic nodes with "peeling" of the hepatic artery to its origin and potentially of the superior mesenteric artery descending along the anterior surface of the aorta [61]. Tumour location also strongly impacts recurrence rate with 23% of liver and 16% of lymph node recurrences in T2b (liver side) GBC despite complementary liver resection [62], whereas recurrences are rare (≈3%) in patients with T2a (peritoneal side) GBC after cholecystectomy alone [63]. Intraoperative gallbladder perforation conveys a very high risk of peritoneal recurrence even after gallbladder extraction in a protective bag, and cannot be considered as curative [64,65]. Liver resection remains controversial for ≥T3 GBC and may consist of IVb-V
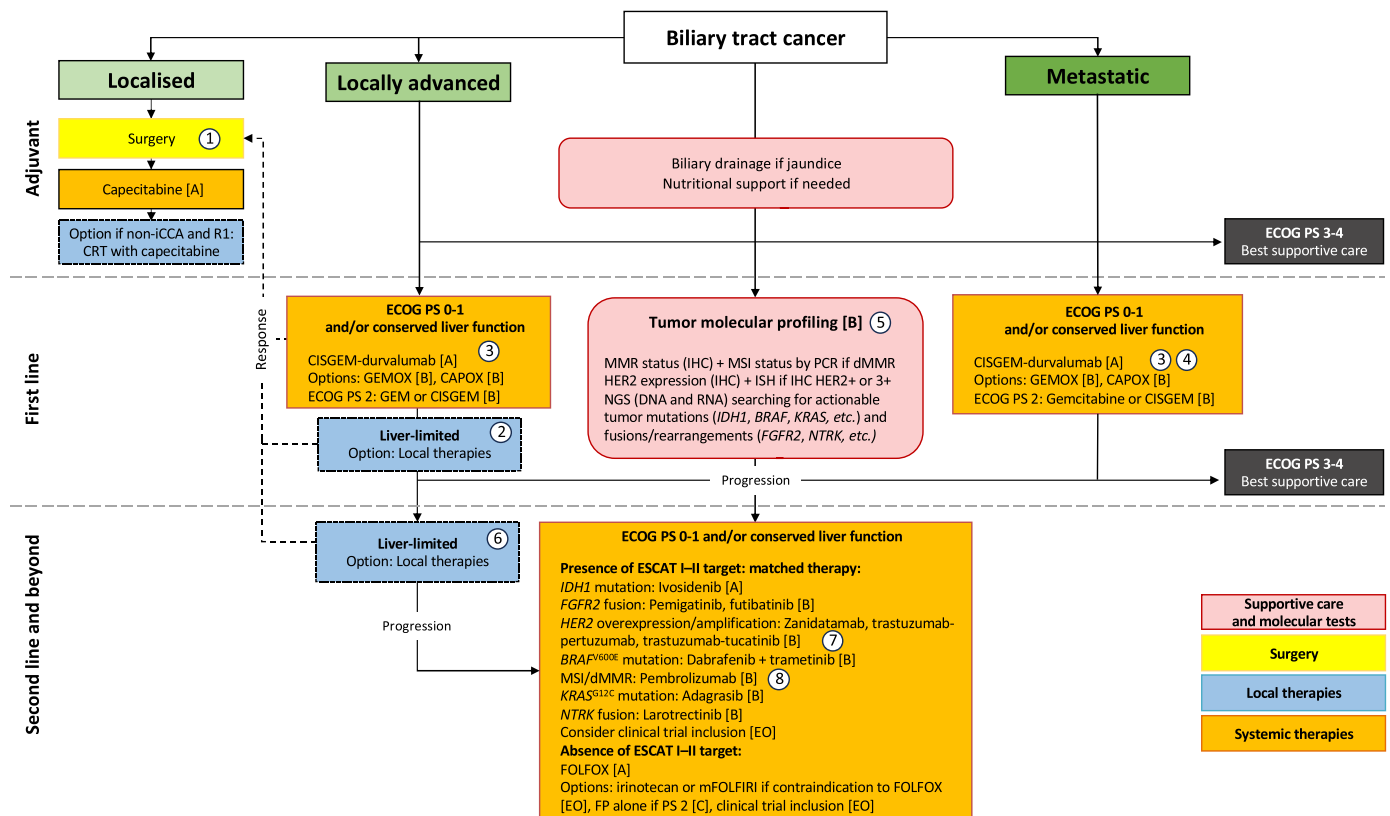
Biliary tract cancer

Localised — **Locally advanced** — **Metastatic**

Adjuant

Surgery ①

Capecitabine [A]

Option if non-iCCA and R1:
CRT with capecitabine

Biliary drainage if jaundice
Nutritional support if needed

ECOG PS 3-4
Best supportive care

First line

ECOG PS 0-1
and/or conserved liver function

CISGEM-durvalumab [A] ③
Options: GEMOX [B], CAPOX [B]
ECOG PS 2: GEM or CISGEM [B]

Liver-limited ②
Option: Local therapies

Tumor molecular profiling [B] ⑤

MMR status (IHC) + MSI status by PCR if dMMR
HER2 expression (IHC) + ISH if IHC HER2+ or 3+
NGS (DNA and RNA) searching for actionable
tumor mutations (*IDH1, BRAF, KRAS, etc.*) and
fusions/rearrangements (*FGFR2, NTRK, etc.*)

ECOG PS 0-1
and/or conserved liver function

CISGEM-durvalumab [A] ③ ④
Options: GEMOX [B], CAPOX [B]
ECOG PS 2: Gemcitabine or CISGEM [B]

ECOG PS 3-4
Best supportive care

Response

Progression

Second line and beyond

Liver-limited ⑥
Option: Local therapies

Progression

ECOG PS 0-1 and/or conserved liver function

Presence of ESCAT I–II target: matched therapy:
IDH1 mutation: Ivosidenib [A]
FGFR2 fusion: Pemigatinib, futibatinib [B]
HER2 overexpression/amplification: Zanidatamab, trastuzumab-
pertuzumab, trastuzumab-tucatinib [B] ⑦
*BRAF*V600E mutation: Dabrafenib + trametinib [B]
MSI/dMMR: Pembrolizumab [B] ⑧
*KRAS*G12C mutation: Adagrasib [B]
NTRK fusion: Larotrectinib [B]
Consider clinical trial inclusion [EO]
Absence of ESCAT I–II target:
FOLFOX [A]
Options: irinotecan or mFOLFIRI if contraindication to FOLFOX
[EO], FP alone if PS 2 [C], clinical trial inclusion [EO]

| Supportive care and molecular tests |
| Surgery |
| Local therapies |
| Systemic therapies |

Fig. 3. Treatment options and recommendations. Grades of recommendation to the GRADE system are figured between brackets. 1-Consideration should be given to: the need for preoperative biliary drainage; assessment of the future remaining liver; complementary surgery in case of incidental stage ≥T1b GBC. In case of clinical and radiological pattern suggestive of resectable p/dCCA where cytology/histology is negative on two occasions, and after cholangioscopy and IgG4 assay, surgical management should not be delayed. Liver transplantation as part of a Mayo Clinic-type preoperative protocol (CRT, exploratory laparotomy/laparoscopy) is accepted in case of N0, ≤ 3 cm, unresectable pCCA (grade B). Percutaneous ablation may be considered for single iCCA < 3 cm without extrahepatic disease if surgical resection is not possible (grade B). SBRT may be discussed for iCCA < 5 cm without extrahepatic disease when surgical resection or percutaneous ablation is not possible (grade C). 2- Hepatic arterial therapies (SIRT, TACE, hepatic arterial chemotherapy) and SBRT may be discussed in unresectable iCCA (or in non-operable patients) without extrahepatic disease (grade C). Hepatic arterial therapies should be combined with systemic chemotherapy as first-line therapy (EO). Surgical resection or percutaneous thermal ablation should be discussed in the event of tumor response in initially unresectable disease. 3- In case of clinical and radiological pattern suggestive of unresectable p/dCCA where cytology/histology is negative on two occasions, and after cholangioscopy and IgG4 assay, the possibility of starting chemotherapy must be validated by the multidisciplinary board (EO). 4- If contraindication for cisplatin: GEMOX; for gemcitabine: CAPOX. 5-Systematic molecular tumor portrait should be performed as soon as first-line treatment is started (or even before, for referral to clinical trials), including: - MMR status (IHC and/or PCR). - HER2 status (IHC; ISH if IHC 2 +). - NGS panel (DNA or RNA) including search for targetable tumor mutations (including *IDH1, BRAF, KRAS*). - Search for fusions/rearrangements (RNA) including *FGFR2* and *NTRK* genes. Tumor molecular profiling on circulating DNA may be considered when no tumor tissue is available, re-biopsy is impossible, and/or tissue tumor molecular profiling failed (EO). In case of a molecular alteration that can be targeted by a non-approved treatment and not accessible by early access or compassionate programs, or in case of multiple molecular alterations, the molecular results should be discussed and validated by an (ideally molecular) multidisciplinary board (EO). 6- Hepatic arterial therapies (SIRT, TACE, hepatic arterial chemotherapy) and SBRT may be discussed in unresectable iCCA (or in non-operable patients) without extrahepatic disease (grade C). Hepatic arterial therapies should be used alone as an alternative treatment after failure of standard systemic therapies in the absence of extrahepatic progression (grade C). Surgical resection or percutaneous thermal ablation should be discussed in the event of tumor response in initially unresectable disease. 7- FOLFOX plus trastuzumab: no consensus agreement from the working group in the absence of Western population data (EO). 8- In the absence of first-line anti-PD1/PDL1 therapy. MSI/dMMR status should be confirmed by both IHC and PCR. Abbreviations: CISGEM, cisplatin/gemcitabine; CRT, chemoradiotherapy; dCCA, distal cholangiocarcinoma; dMMR, deficient DNA mismatch repair; ECOG, Estern Cooperative Oncology Group; EO, expert opinion; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FOLFOX, leucovorin/fluorouracil/oxaliplatin; FP, fluoropyrimidine; GBC, gallbladder cancer; GEM, gemcitabine; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; ISH, in situ hybridisation; MMR, DNA mismatch repair; MSI, microsatellite instability; Nal-Iri-5FU-LV, liposomal irinotecan/fluorouracil/leucovorin; NGS, next-generation sequencing; pCCA, perihilar cholangiocarcinoma; PCR, polymerase chain reaction; PS, performance status; R1, microscopically positive resection; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy; TACE, trans-arterial chemo-embolisation.

bi-segmentectomy, or tri-segmentectomy or meso-(I-IV-V-VIII) hepatectomy for GBC invading the hepatic pedicle. Direct invasion of colon, duodenum or liver does not absolutely contraindicate resection. Common bile duct resection is often performed and facilitates hepatic pedicle lymph node dissection in ≥T3 GBC.

After incidental diagnosis of GBC during cholecystectomy, cholecystectomy alone is sufficient for Tis-T1a GBC (5-year OS, 95–100%) [37,66]. For later stages, early re-resection is recommended due to the high risk of local and metastatic spread [67], especially in T1b-T2 stages [68–70], for which it significantly reduces the risk of recurrence and increases OS [48,49,55]. However, a role for delayed re-resection has been suggested in patients without unresectable disease after restaging by CT and laparoscopy at 3 months after index cholecystectomy [47].

3.3. Percutaneous tumour ablation techniques

To date, no study has prospectively evaluated percutaneous tumour ablation techniques (e.g., radiofrequency, cryotherapy, irreversible electroporation, microwave) in BTCs. These techniques can only be considered for single (or few), small (<3 cm) iCCA lesions, and are

Table 3
Biliary tract cancers: therapeutic recommendations and options.

Recommendations & *Options*				Level of evidence
Localised/resectable BTC				
Neoadjuvant treatment		Should only be performed in the context of a clinical trial.		C
		If an initially inoperable tumour responds to first-line therapy, resection/ablation should be re-discussed.		
Surgery/ transplantation/ ablation	**iCCA**	R0 resection (margins ≥10 mm) of invaded liver segments + lymphadenectomy (≥6 nodes)		C
		Single iCCA < 3 cm, no extrahepatic disease: percutaneous thermal ablation if surgery not possible		*C*
		iCCA < 5 cm, no extrahepatic disease: SBRT may be discussed if resection/ablation not feasible		*C*
	pCCA	En-bloc resection of CBD and superior biliary convergence + hepatectomy including segments I and IVb + pedicle lymphadenectomy ± vascular resection/reconstruction		C
		≤ 3 cm, N0 and unresectable: liver transplantation acceptable as part of a Mayo Clinic-type preoperative protocol (CRT, exploratory laparotomy / laparoscopy)		*B*
	dCCA	CBD middle third: CBD resection + pedicle lymphadenectomy		C
		CBD lower third: pancreatoduodenectomy + pedicle lymphadenectomy		C
	GBC	Tis, T1a: cholecystectomy (lymph node dissection not recommended if gallbladder is intact)		B
		T1b, T2: cholecystectomy + resection of segments IVb-V (tumour invading only the gallbladder bed and <20 mm) + pedicle lymph node dissection		B
		T3 or N + : benefit of surgery not demonstrated. Cholecystectomy + MBD resection + resection of invaded liver segments + pedicle lymphadenectomy ± vascular resection/reconstruction		*B*
Adjuvant treatment		Adjuvant capecitabine within 16 weeks after surgery and for 24 weeks (8 cycles) in ECOG PS 0-1 patients with iCCA/pCCA/dCCA/ GBC, > pT1, R0 or R1		B
		Adjuvant CRT with capecitabine after 4 to 6 months of adjuvant capecitabine may be discussed after R1 resection of pCCA/dCCA/GBC		*EO*
Locally advanced (unresectable) and metastatic BTC				
Biliary drainage		Endoscopic and/or percutaneous drainage if symptoms related to jaundice or if needed before starting antitumor therapy		A
Molecular tumour profiling		Systematic tumour molecular profiling within first line, to identify:		B
		1. MSI/dMMR (IHC, PCR; MSI/dMMR on NGS should be confirmed by IHC/PCR)		
		2. HER2 overexpression/amplification (IHC, ± ISH if IHC 2 +; *HER2* amplification on NGS should be confirmed by IHC/ISH)		
		3. Targetable mutations (including *IDH1, BRAF, KRAS*) (DNA or RNA NGS)		
		4. Targetable fusions/rearrangements (including *FGFR2* and *NTRK*) (RNA NGS)		
First line		Always consider inclusion in a clinical trial		EO
	Preserved liver function	**PS 0-1**	CISGEM + durvalumab (EAP) or pembrolizumab (no access)	A
			CISGEM if contraindication to immunotherapy	
			GEMOX if contraindication to cisplatin	*B*
			CAPOX if contraindication to gemcitabine	
			Hepatic intra-arterial treatments (SIRT, TACE, hepatic arterial chemotherapy) and SBRT may be discussed in unresectable iCCA (or in inoperable patients) without extrahepatic disease in addition to standard systemic therapy	*C*
		PS 2	Single-agent gemcitabine (or CISGEM)	B
	Altered liver function or PS 3-4		Exclusive BSC	EO
Second line and beyond		Always consider inclusion in a clinical trial		EO
	Targetable tumour molecular alteration (and PS 0-2)			
		IDH1 mutation: ivosidenib (reimbursed)		A
		FGFR2 fusion/rearrangement: pemigatinib (reimbursed), futibatinib (no access)		B
		HER2 amplification/overexpression: zanidatamab (CAP), trastuzumab + pertuzumab (no access), trastuzumab + tucatinib (no access), FOLFOX + trastuzumab (no access; no expert consensus)		B
		BRAF^{V600E} mutation: dabrafenib + trametinib (no access)		B
		MSI/dMMR: pembrolizumab (no access) (if no anti-PD1/PDL-1 therapy in first line)		B
		KRAS^{G12C} mutation: adagrasib (no access)		C
		NTRK fusion: larotrectinib (no access)		B
	No targetable tumour molecular alteration			
	Preserved liver function	**PS 0-1**	FOLFOX	A
			mFOLFIRI (or irinotecan) if contraindication to FOLFOX	*EO*
			Hepatic arterial treatments (SIRT, TACE, hepatic arterial chemotherapy) and SBRT may be discussed in unresectable iCCA (or in inoperable patients) without extrahepatic disease	*C*
		PS 2	Single-agent fluoropyrimidine	C
	Altered liver function or PS 3-4		Exclusive BSC	EO
Secondary resection/ ablation		*Resection/ablation should be discussed in case of tumour response of initially unresectable disease*		*EO*

Options are figured in italics.

Abbreviations: best supportive care, BSC; CAP, Compassionate Access Programme; CBD, common bile duct; CISGEM, cisplatin and gemcitabine; CRT, chemo-radiotherapy; dCCA, distal cholangiocarcinoma; EAP, Early Access Programme; EO, Experts' opinion; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO, European Society of Medical Oncology; FGFR2, fibroblast growth factor receptor 2; GBC, gallbladder carcinoma; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IDH1, isocitrate dehydrogenase 1; IHC, immunohistochemistry; ISH, in situ hybridisaiton; MSI/dMMR, microsatellite instability/mismatch repair deficiency; N/A, not available; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; pCCA, perihilar cholangiocarcinoma; PCR, polymerase chain reaction; PD1, programmed cell death 1; PS, Eastern Cooperative Oncology Group (ECOG) performance status; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy; TACE, trans-arterial chemo-embolisation.

generally performed in patients considered as non-suitable for surgery (e.g., post-resection recurrence, liver cirrhosis). In a systematic review (645 patients), radiofrequency ablation was the most commonly used technique (7/15 studies) [71]. Median tumour size was 27 mm (range, 15–44), complete response rate was 93.9%, and median OS (mOS) was 30.2 months (95% confidence interval [CI]: 21.8–38.6).

3.4. Liver transplantation

In a retrospective American multicentre study of 287 patients with

unresectable pCCA (mostly with underlying primary sclerosing cholangitis), the 5-year intention-to-treat (ITT) OS rate was 53% after neo-adjuvant chemoradiotherapy, brachytherapy, chemotherapy, then exploratory laparotomy, and finally liver transplantation (Mayo Clinic protocol) [72]. A meta-analysis of 20 studies (428 patients) reported 5-year OS rates after liver transplantation for unresectable pCCA of 65.1% and 31.6% with and without neoadjuvant chemoradiotherapy, respectively (3-year recurrence rates: 51.7% and 24.1%, respectively) [73]. Liver transplantation following this preoperative protocol may be discussed for unresectable pCCA, taking into account the complexity of this therapeutic program, the high rate of radiation-induced post-operative vascular complications and the low ITT benefit resulting from the strict selection of candidates.

3.5. Adjuvant setting

The results of five randomised trials assessing adjuvant chemotherapy are available to date. The Asian BCAT [74] and the French PRODIGE 12 [75] randomised trials failed to demonstrate a significant improvement of relapse-free survival (RFS) and mOS with gemcitabine and gemcitabine-oxaliplatin (GEMOX), respectively, compared to surveillance. The British BILCAP trial randomised 447 patients to adjuvant capecitabine (8 cycles, 24 weeks) or surveillance [76]. The OS benefit (primary endpoint) in the primary ITT analysis (mOS: 51.1 vs. 36.4 months; hazard ratio (HR): 0.81; p = 0.097) reached statistical significance only after a pre-specified adjustment on sex, histological grade and nodal status (HR: 0.71; p = 0.01). The RFS benefit (median: 24.4 vs. 17.5 months; HR: 0.75; p = 0.033) was only observed during the first 24 postoperative months. Tolerance was acceptable, and no deleterious effect on quality of life was observed. The South Korean phase II randomised STAMP trial failed to demonstrated a benefit of CISGEM over capecitabine after resection in 101 patients with N + pCCA or dCCA in DFS (primary endpoint; median: 14.3 vs. 11.1 months; HR: 0.96 [CI 0.71–1.30]; p = 0.43) or OS [77]. The Japanese randomised phase III trial ASCOT compared in 440 patients S-1, an oral fluoropyrimidine widely used in Asia but not validated in the European population, with surveillance after R0 resection of BTC. A benefit in OS (primary endpoint) was observed (HR: 0.69 [CI 0.51–0.94]; 3-year OS: 77.1% vs. 67.6%; p = 0.008), even though RFS was not significantly improved with S-1 (HR: 0.80 [CI 0.61–1.04]; 3-year RFS: 62.4% vs. 50.9%; p = 0.088) [78]. This study, although not transposable to the European population, reinforces the rationale for fluoropyrimidines in the adjuvant setting.

No prospective randomised trials assessing adjuvant radiotherapy or chemoradiotherapy are available. Two meta-analyses of published data (mainly retrospective or registry studies) suggested a greater benefit of chemoradiotherapy (and chemotherapy) over radiotherapy alone, the benefit of adjuvant therapy overall seeming greater in N + (OR: 0.49; p = 0.004) or R1 (OR: 0.36; p = 0.002) tumours [79,80]. A single-arm phase II trial evaluated 3 months of adjuvant gemcitabine-capecitabine combination chemotherapy followed by chemoradiotherapy with capecitabine in patients with resected extrahepatic CCA or GBC. Similar results in mOS (R0, 34 months; R1, 35 months) and 2y-OS between R0 and R1 tumors suggested a stronger benefit after R1 resection [81]. Grade 3 and 4 adverse events were observed in respectively 52% and 11% of patients.

4. Management of advanced disease

The primary objective of advanced disease management is to maintain or improve quality of life (e.g., pain control, biliary drainage, nutritional support) and relies in any circumstances on best supportive care (BSC).

4.1. Palliative surgery

Macroscopically incomplete resections (R2 surgical margin status) have no palliative impact. Surgical biliary diversions (and transtumour intubations) are not superior to endoscopic or percutaneous biliary drainage [82] and convey significant mortality (exceeding 25% in several series) and morbidity. Non-surgical drainage techniques should be preferred even though surgical bypass may be considered in selected patients with relatively long survival expectancy and no possibility for optimal endoscopic or percutaneous drainage.

4.2. Endoscopic procedures

Biliary drainage is indicated in case of symptoms related to biliary obstruction (e.g., pruritus, cholangitis) and when necessary before starting antitumor therapy. Biliary drainage should be performed in a centre with endoscopic and interventional radiology expertise.

Cholangio-MRI is the examination of choice for planning biliary drainage, which must be as complete as possible and prioritize functional areas. Perioperative antibioprophylaxis is recommended [83]. The stenting procedure depends on the site and extent of the tumour(s) and is ideally performed by ERC [84,85]. Uncovered self-expandable metal stents are cheaper than covered metal stents and stay patent longer than plastic stents [86]. Hilar uncovered metallic stenting must be strictly reserved to cases for which surgery is definitively excluded. Unilateral hilar stenting, which seems as effective as bilateral stenting, must be considered with caution, as it may hamper subsequent procedures [87]. Local tumour destruction by endoscopic radiofrequency ablation may be discussed in cases of stenting difficulties or early tumoral stent obstruction [88,89]. When the endoscopic retrograde route fails or is impossible due to previous surgery, percutaneous radiological stenting or endoscopic ultrasound-guided choledocoduodenal or gastrohepatic stenting should be considered.

The analgesic efficacy of celiac neurolysis has not been demonstrated in BTCs.

4.3. Palliative (chemo)radiotherapy

No randomised controlled trial has demonstrated a survival benefit of radiotherapy, brachytherapy or chemoradiotherapy over biliary drainage alone in locally advanced BTCs. The randomised phase II-III trial FFCD-9902 compared chemoradiotherapy (50 Gy, 5-fluorouracil [5-FU] and cisplatin) to systemic chemotherapy with GEMOX in patients with unresectable, locally advanced BTC [90]. The trial was closed before completion due to slow recruitment (34 inclusions/72 scheduled), thereby reducing its statistical power. Survival was numerically shorter with chemoradiotherapy compared to chemotherapy (median progression-free survival [mPFS]: 5.8 vs. 11.0 months; HR: 0.65 [CI 0.32–1.33]; mOS was 13.5 vs. 19.9 months; HR: 0.69 [CI 0.31–1.55]).

A non-randomised multicentre study in 39 patients with unresectable iCCA showed that high-dose hypofractionated proton beam therapy achieved a 2-year OS rate of 46.5% (mOS, 22.5 months) and a 2-year PFS rate of 26% [91]. A retrospective study of 79 patients showed that higher doses of radiation therapy (biologic equivalent dose >80.5 Gy) were associated with a higher 3-year OS (73% vs. 38%, p = 0.017) and local control (78% vs. 45%, p = 0.04) rates compared to lower doses [92]. Stereotactic body radiation therapy can also be proposed for single tumours (<5 cm in diameter ideally) considered as non-operable and not accessible to percutaneous thermal ablation [93–96].

4.4. Hepatic intra-arterial therapies

Hepatic arterial treatments (e.g., hepatic arterial chemotherapy, transarterial embolisation, transarterial chemoembolisation [TACE], selective internal radiation therapy [SIRT]) may be proposed as a first-line treatment or after tumour progression under systemic treatment

for patients with unresectable iCCA; however, the level of evidence is low, mostly based on non-randomised, small, single-centre or retrospective studies with heterogeneous populations regarding previous treatments, size and number of lesions, and presence of macrovascular invasion or extrahepatic disease [71]. The results of the only available randomised trial (TACE with irinotecan-loaded beads plus systemic gemcitabine-cisplatin vs. systemic gemcitabine-cisplatin alone) were in favour of the combination in terms of secondary resection/ablation rate (25% vs. 8%, p < 0.005) and OS (mOS: 33.7 vs. 12.6 months, p = 0.048) [97]. In a meta-analysis collecting data on SIRT (27 studies, 1232 patients), TACE (conventional or with drug eluting-beads; 22 studies, 1145 patients) and hepatic arterial chemotherapy (16 studies, 331 patients), ORR was 23.4%, 26.3%, and 41.3%, mPFS was 7.8, 15.0, and 10.1 months, and mOS was 14.1, 15.9, and 21.3 months, respectively [65]. Concomitant systemic chemotherapy was associated in 29.9%, 74.4%, and 96% of patients, respectively, making comparisons difficult. In a meta-analysis of six prospective studies, the combination of gemcitabine-platinum chemotherapy with SIRT significantly improved PFS (median: 8.4 vs. 4.3 months; HR: 0.52 [CI 0.31–0.89]; p < 0.001) and OS (median: 21.7 vs 15.9 months; HR: 0.59 [CI 0.34–0.99]; p = 0.049) compared to chemotherapy alone [98]. SIRT with yttrium 90 (Y90) microspheres (Therasphere®, Biocompatibles UK Limited, BTG International Group, UK) is reimbursed in France for the first-line treatment, with or without systemic chemotherapy, of patients with unresectable or recurrent iCCA provided that the following criteria are fulfilled: no extrahepatic disease; tumour burden < 50%; preserved performance status (PS; 0–1 in combination with chemotherapy or 0–2 if Therasphere® alone); and preserved liver function.

4.5. Systemic treatments

4.5.1. First-line chemotherapy and immunotherapy

In 2010, the ABC-02 phase III trial demonstrated the superiority of the cisplatin-gemcitabine combination (CISGEM) administered for 24 weeks over gemcitabine alone (mOS: 11.7 vs. 8.1 months; HR: 0.64 [CI 0.52–0.80]; p < 0.001), regardless of tumour stage (locally advanced or metastatic) and location [99]. In subgroup analysis, the combination was only beneficial in patients with ECOG PS 0–1 (88% of the patients). Safety of CISGEM was acceptable, and the low doses of cisplatin (25 mg/m^2 on day [D]1 and D8, every 3 weeks) allow outpatient administration with light hydration. Consistent results were observed in Asian trials [100,101]. Of note, gemcitabine maintenance after 6 months of CISGEM, although frequently administered worldwide, has not been prospectively validated so far [102,103].

All trials of triple chemotherapy regimens (e.g., FOLFIRINOX [104], CISGEM-nab-paclitaxel [105]) failed to demonstrate a superiority over CISGEM so far, with the exception of the combination of CISGEM to the oral fluoropyrimidine S-1 in a Japanese randomised phase III trial [106].

Capecitabine-oxaliplatin (CAPOX) and GEMOX regimens can be used instead of CISGEM in cases of contraindication, based on randomised phase II trials and cohort studies [90,107–111].

Two international, randomised, placebo-controlled phase III trials demonstrated an OS benefit of the addition of immunotherapy to CIS-GEM with the anti-programmed cell death ligand-1 (PDL-1) durvalumab (TOPAZ-1 trial [112]; mOS: 12.9 vs. 11.3 months; HR: 0.76 [CI 0.64–0.91]) or the anti- programmed cell death-1 (PD1) pembrolizumab (KEYNOTE-966 trial [113]; mOS: 12.7 vs. 10.9 months; HR: 0.83 [CI 0.72–0.95]) over CISGEM alone, leading to their approval by the FDA and – for durvalumab only to date – by the EMA. Durvalumab is currently available in France through an early access program.

4.5.2. Chemotherapy in second line and beyond

In 2019, the ABC-06 study – the only randomised phase III trial of second-line chemotherapy in BTC to date – showed an ORR of 5% and a modest OS benefit of the combination of 5-FU and oxaliplatin (FOLFOX regimen) over BSC alone (mOS: 6.2 vs. 5.3 months; HR: 0.69 [CI

0.50–0.97]; p = 0.031) in 162 patients with advanced BTC whose disease had progressed after first-line CISGEM and with an ECOG PS of 0 to 1 [114]. In a South Korean randomised phase II trial in 118 patients with advanced BTC and an ECOG PS of 0 to 2, no difference was found between mFOLFIRI (5-FU plus irinotecan) and mFOLFOX in terms of ORR (4.0 vs. 5.9%; p = 0.663), mPFS (2.1 vs. 2.8 months; p = 0.97), or mOS (5.7 vs. 6.3 months, p = 0.68) [115]. The combination of 5-FU and nanoliposomal irinotecan (NALIRI) was superior to 5-FU alone in terms of ORR (12.5% vs. 3.5%; p = 0.04), PFS (median: 4.2 vs. 1.7 months; HR: 0.61 [CI 0.44–0.86]; p = 0.004) and OS (median: 8.6 vs. 5.3 months; HR 0.68 [CI 0.48–0.95]; p = 0.02) in the South Korean randomised phase II trial NIFTY [116], but not in the German randomised phase II trial NALIRICC [117] (mPFS: 2.6 vs. 2.3 months; HR: 0.87 [CI 0.56–1.35]; mOS: 6.9 vs. 8.2 months; HR: 1.08 [CI 0.68–1.72]), even though ORR was higher (14.3% vs. 3.9%); grade 3 or higher adverse events were more frequent in the combined arm (70.8% vs. 50%).

No randomized study has evaluated chemotherapy in third line and beyond in BTC to date.

4.5.3. Molecular profiling and personalized medicine

All randomised trials reported to date that evaluated the combination of chemotherapy with a targeted therapy in unselected patients with advanced BTC failed to demonstrate an OS benefit [109,118–121]. The richness of BTCs, notably iCCA, in tumour gene alterations accessible to therapeutic targeting, and the clinical successes observed with several targeted therapies, some of which are already available, plead for systematic molecular tumour profiling of advanced BTCs [122,123]. Molecular tumour profiling should ideally be performed during first line, as: 1) oncogenic driver alterations occur early during tumour oncogenesis, and persist throughout the course of the disease, without significant changes in the absence of selection by targeted therapy [124]; 2) the molecular tumour profiling turnaround time might not be compatible with the high attrition rate (up to 70%) from one line to another in BTC [125]. Molecular tumour profiling must be able to detect gene fusions/rearrangements, ideally by RNA NGS, and mutations of therapeutic interest according to the ESMO Scale for Clinical Actionability of Molecular Target (ESCAT) classification [126,127]. Besides molecular profiling, MSI/dMMR tumour status should be systematically searched for by IHC and/or polymerase chain reaction (PCR) given the prospects for immunotherapy, as well as HER2 overexpression/amplification (IHC ± ISH). The main actionable alterations, their matched targeted therapies, and their accessibility in US, Europe and France are detailed in Table 4.

4.5.3.1. Isocitrate dehydrogenase 1 (IDH1). Isocitrate dehydrogenase 1 (IDH1) mutations are found in approximately (and almost exclusively) 15% of patients with advanced iCCA [128]. The results of the ClarIDHy study – the only randomised Phase III trial of targeted therapy in BTC to date – showed a significant improvement with ivosidenib, an oral IDH1 inhibitor, in PFS (the primary study endpoint) compared to placebo (median: 2.7 vs. 1.4 months; HR: 0.37 [CI 0.25–0.54]; p < 0.001) in 185 patients with an IDH1-mutated advanced CCA who previously progressed after one or two lines of chemotherapy and an ECOG PS of 0 or 1 [129]. An OS benefit was observed only after a statistical analysis taking into account the crossover of patients who received ivosidenib after progression in the placebo arm (71% of patients; mOS: 10.3 vs. 5.1 months; HR: 0.49; p < 0.001) [130]. Ivosidenib has been approved by FDA and EMA in adult patients with IDH1-mutated, previously treated, locally advanced or metastatic cholangiocarcinoma, and is reimbursed in France (albeit in third line only).

4.5.3.2. Fibroblast growth factor receptor 2 (FGFR2). Fusions and rearrangements of the fibroblast growth factor receptor 2 (FGFR2) gene are observed in approximately (and almost exclusively) 15% of iCCA [131]. Several non-randomised phase I/II or II trials showed the activity of oral

Table 4
Precision medicine in cholangiocarcinoma: ESCAT-I alterations and their matched targeted therapies.

Gene alteration	ESCAT tier	Frequency Preferential BTC subtypes	Drug name [key study reference]	Approval (BTC) FDA	Approval (BTC) EMA	Availability in France
IDH1 **mutation**	I-A	10-20% iCCA	Ivosidenib[129]	Yes	Yes	EAP
FGFR2 **fusions/rearrangements**	I-B	10-15% iCCA	Pemigatinib[132]	Yes	Yes	Reimbursed
			Futibatinib[138]	Yes	Yes	-
HER2 **overexpression/amplification**	I-C	10-15% pCCA/dCCA/GBC > iCCA	Trastuzumab-pertuzumab[140]	-	-	-
			FOLFOX-trastuzumab[142]	-	-	-
			Trastuzumab-deruxtecan [141]	Yes[a,c]	-	-
			Trastuzumab-tucatinib [144]	-	-	-
			Zanidatamab [160]	Yes[a]	Yes[b]	CAP
MSI/dMMR	I-C	< 1%	Pembrolizumab [146]	Yes[c]	Yes[c]	Denied
NRTK **fusions**	I-C	< 1%	Larotrectinib [148]	Yes[c]	Yes[c]	-
			Entrectinib [149]	Yes[c]	Yes[c]	-
RET **fusions**	I-C	1%	Pralsetinib [154]	-	-	-
			Selpercatinib [153]	Yes[c]	-	-
BRAF[V600E] **mutation**	II-B	< 5%	Dabrafenib-Trametinib [156]	Yes[c]	-	-
KRAS[G12C] **mutation**	II-B	1%	Adagrasib [161]	-	-	-

ESCAT tier, FDA/EMA approvals and availability in France are given as of December 2023.

Abbreviations: BTC, biliary tract cancer; CAP, Compassionate Access Program; dCCA, distal cholangiocarcinoma; EAP, Early Access Programme; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO, European Society of Medical Oncology; FDA, Food and Drug Administration; FGFR2, fibroblast growth factor receptor 2; GBC, gallbladder carcinoma; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IDH1, isocitrate dehydrogenase 1; MSI/dMMR, microsatellite instability/mismatch repair deficiency; NTRK, neurotrophic tyrosine receptor kinase; pCCA, perihilar cholangiocarcinoma.

[a] Breakthrough therapy designation.
[b] Orphan designation.
[c] Tumour-agnostic approval.

pan-FGFR or FGFR2 inhibitors in patients with advanced CCA harbouring a *FGFR2* fusion or rearrangement and previously treated by at least one line of systemic therapy [132–137]. In particular, pemigatinib and futibatinib respectively showed ORR of 35.5% and 42%, mPFS of 6.9 and 9.0 months, and mOS of 21.1 and 21.7 months in the single-arm phase II trials FIGHT-202 and FOENIX-CCA2 including 107 and 103 patients with *FGFR2*-rearranged CCA naive to FGFR inhibitors [132, 138]. Tinengotinib, a new class FGFR2 inhibitor with specific binding to FGFR2 overcoming acquired resistances showed promising results with ORR of 34% and mPFS of 6.9 months in patients pre-treated by FGFR inhibitors [139]. Pemigatinib and futibatinib have been approved by FDA and EMA.Only pemigatinib is reimbursed in France to date. The phase III trials FIGHT-302 (first-line pemigatinib versus CISGEM) and FIRST-308 (tinengotinib versus investigator's choice standard chemotherapy in patients with *FGFR2*-altered CCA refractory to FGFR inhibitors) are ongoing.

4.5.3.3. Human epidermal growth factor receptor 2 (HER2). Alterations in the human epidermal growth factor receptor 2 *(HER2)* gene (e.g. amplification, overexpression, or more rarely mutations) are observed in around 15% of BTCs, mostly in GBC, pCCA, dCCA, and ampullary adenocarcinomas [131]. Several non-randomised phase I/II or II trials in patients with chemorefractory, *HER2*-overexpressed/amplified, advanced BTC showed ORR ranging from 23% to 47%, mPFS of 4.0 to 5.5 months, and mOS of 7.1 to 10.9 months with various HER2 inhibition approaches [125], including the combination of the anti-HER2 monoclonal antibodies trastuzumab and pertuzumab [140]; the HER2 antibody-drug-conjugate trastuzumab-deruxtecan [141]; the combination of trastuzumab and modified FOLFOX [142]; the bispecific anti-HER2 antibody zanidatamab [143], which is currently available in France through a compassionate access programme; and the combination of trastuzumab with tucatinib [144]. Of note, HER2 inhibitors are currently tested in the first-line setting. A single-arm phase II trial showed an ORR of 55.5% and a mPFS of 7 months (mOS not specified; median follow up of 17.3 months) with the frontline combination of trastuzumab and CISGEM in 90 chemonaive BTC patients [145]. The phase III trial HERIZON-BTC assessing the addition of zanidatamab to first-line CISGEM-durvalumab is ongoing.

4.5.3.4. Microsatellite instability-high/mismatch repair deficiency. MSI-high/dMMR, either constitutional (Lynch syndrome) or acquired (sporadic), is observed in approximately 2% of advanced BTCs [131]. A non-randomised phase II trial of immunotherapy with pembrolizumab (anti-PD-1 monoclonal antibody) including 22 previously treated, MSI/dMMR, advanced BTC patients with an ECOG PS of 0 or 1 showed an ORR of 40.9%, similar to the rate (34.3%) observed in the overall trial population of 233 patients with advanced, non-colorectal MSI/dMMR cancer [146]. Pembrolizumab is FDA and EMA approved for MSI/dMMR BTCs, but not reimbursed in France.

4.5.3.5. Neurotrophic tropomyosin receptor tyrosine kinase (NTRK). Fusions involving neurotrophic tropomyosin receptor tyrosine kinase *(NTRK)* − 1, − 2 or − 3 genes are observed in < 1% of BTCs [147]. In a phase I-II trial evaluating the oral NTRK inhibitor larotrectinib in 55 patients with *NTRK* fusion-positive advanced cancer (17 tumour types), the ORR was 75%; an objective tumour response was observed in one of the two CCA patients included [148]. In a pooled analysis of three phase I-II trials with the oral NTRK inhibitor entrectinib, the ORR was 57%, including the only CCA patient included [149]. Larotrectinib and entrectinib have been approved by FDA and EMA for the treatment of solid tumours with an *NTRK* gene fusion, but are currently not reimbursed for adults in France (larotrectinib is only reimbursed in paediatric indications). According to recent European recommendations, NGS (preferably RNA), or IHC followed by sequencing of positive cases, should be performed in unselected populations where *NTRK* fusions are uncommon, such as patients with BTC [150].

4.5.3.6. Rearranged during transfection (RET). Rearranged during transfection gene *(RET)* fusions are found in various cancers, including 1% of BTC cases [151,152]. Non-randomised phase I/II trials showed the activity of the two oral RET inhibitors pralsetinib and selpercatinib in patients with *RET* fusion-positive solid tumours including BTC, with ORR of 57% and 43.9%, mPFS of 7.0 and 13.2 months, and mOS of 14.0 and 18.0 months, respectively [153,154]. Their EMA approval is currently restricted to *RET* fusion-positive advanced non small-cell lung cancer (NSCLC) for selpercatinib and praseltinib and thyroid cancer including medullary thyroid cancer for selpercatinib; selpercatinib is

currently reimbursed in France for NSCLC and medullary thyroid cancer only.

4.5.3.7. v-Raf murine sarcoma viral oncogene homolog B (BRAF).

v-Raf murine sarcoma viral oncogene homolog B *(BRAF)* mutations, mostly V600E, are observed in approximately 5% of BTCs [155]. In the non-randomised phase II trial ROAR assessing the combination of the oral BRAF inhibitor dabrafenib and the MEK inhibitor trametinib in 43 patients with *BRAF^{V600E}*-mutated BTC. ORR, mPFS and mOS were respectively 58.1%, 9.0 and 13.5 months [156,157]. Agnostic FDA approval has been obtained; however, no approval was grantedby the EMA nor access programme in France for the treatment of *BRAF^{V600E}*-mutated BTC.

4.5.3.8. V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS).

V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog *(KRAS)* mutations occur in approximately 20% of BTCs, of which *KRAS^{G12C}* mutations, the only currently targetable ones, account for approximately 5% of mutations (i.e. 1% of BTCs) [158]. In a phase I/II trial, the oral selective *KRAS^{G12C}* inhibitor adagrasib showed promising antitumor efficacy in 63 patients with *KRAS^{G12C}* mutated tumours including 12 patients with BTC. ORR, mPFS and mOS were respectively 47.1%, 8.6, and 15.1 months in the BTC cohort [159]. To date, there are no activity data in BTCs for the *KRAS^{G12C}* inhibitor sotorasib, which has been approved in Europe for the treatment of pre-treated, *KRAS^{G12C}*-mutated advanced NSCLC.

Even though molecular profiling is widely studied and brought several new targeted therapeutic options to BTC patients, available data to date are derived from non-randomised studies (with the exception of the CLARIDHY trial for *IDH1*-mutated cholangiocarcinoma). Moreover, randomized trials are in first line are difficult to conduct owing to the rarity of the molecularly defined BTC subpopulations and the turnaround time of molecular profiling. The PRODIGE 80 SAFIR-ABC10 phase 3 trial (NCT05615818) will attempt to prove the feasibility and the benefit of an early molecular profiling guiding different maintenance targeted therapeutic options in patients responding or stable under CISGEM-durvalumab. To finish, further BTC-specific prospective studies are expected in other tumour gene alterations such as *BRCA, MET, HER3, BAP1, ARID1A, PIK3CA, NRG1* or *MDM2* to widen the panel of therapeutic options for patients.

5. Follow-up and long-term considerations

The value of repeat serum determinations of one or more tumour markers for follow-up during treatment or post-therapy monitoring has not been demonstrated. No standard surveillance protocol exists in BTCs after curative-intent resection. Clinical examination and imaging (thoraco-abdomino-pelvic CT or thoracic CT plus abdominal MRI) every 3 to 6 months for 2 years, then every 6 months for up to 5 years may be proposed, only to patients able to tolerate treatment for tumour recurrence (expert consensus).

Ethics approval statement

N/A.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Gael Roth declares consulting or advisory role or invitation as a speaker for Servier, AstraZeneca, Bristol-Myers Squibb, MSD, Amgen, Ipsen, Accord Healthcare, Pierre Fabre, Incyte, Netris Pharma and Alpha Tau, as well as travel accommodations, or expenses from Servier, AstraZeneca, Bristol Myers Squibb, MSD, Roche, Amgen, Viatris, Pierre Fabre and Ipsen. Research funding by Genoscience Pharma, Netris Pharma.

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All remaining authors have declared no conflicts of interest.

Data avail-ability statement

N/A.

Patient consent statement

N/A.

Permission to reproduce material from other sources

N/A.

Clinical trial registration

N/A.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114000.

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