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Authors: Medical Oncology Department, Hospital Universitario Vall D'Hebron, Barcelona, Spain. tmacarulla@vhio.net.

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disease. Surgery is the only potentially curative therapy in localized stages; however, disease recurrence is common and adjuvant chemotherapy appears to improve survival. Upfront systemic chemotherapy with immunotherapy is the treatment of choice in unresectable locally-advanced and metastatic disease. Inroads made in understanding its molecular biology has enabled new therapeutic targets to be identified with current indications and encouraging results that could further improve BTC patients' survival and quality of life.

Cholangiocarcinoma (CCA) that includes intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA) and extrahepatic cholangiocarcinoma (eCCA), gallbladder cancer (GBC), and ampullary cancer (AoVC) constitute the group of malignancies known as biliary tract cancer (BTC). They account for 1% of all cancers, 3% of gastrointestinal cancers, and typically occur between 65 and 84 years of age. Incidence is higher among males than females except for GBC [1].

Epidemiologic research of BTC is limited by the fact that they involve distinct locations and are known to be under-reported and misclassified in cancer registries. Challenges in registering them hinder their true incidence to be estimated. The highest age-standardized incidence rate (ASIR) of BTC was reported in Chile (14.3/100,000 inhabitants and year) and the lowest in Vietnam [1]. BTC is increasing in Western countries (0.3–3.5 cases per 100,000 population in Europe) and the greatest annual percentual change was witnessed in iCCA whose incidence has grown by more than 140% in the last forty years [2]. This trend is higher in younger adults (20–54 years) [3]. In Spain, the ASIR of BTC was 2.9 in 2008–2012 with a projected 2024 incidence of 2358 cases [1 , 2]. GBC and AoVC have the highest and lowest incidence rates, respectively, though iCCA could surpass GBC presently [4]. pCCA account for 60% of all CCA [5], albeit up to 92% of all pCCA known to be incorrectly coded as iCCA. In contrast, the drop in “non-specified biliary tract cancer” reflects more precise diagnosis nowadays and in addition to the decrease in cancer of unknown primary [4].

The divergent epidemiology trends observed for iCCA and eCCA suggest different etiologies. While the etiology of BTC is unknown in most Western countries, risk factors for CCA include many predisposing conditions as a result of chronic inflammation, as well as socioeconomic deprivation [6]. In Asian countries, patients with hepatobiliary flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*) or hepatolithiasis are at higher risk. Tobacco, alcohol, non-alcoholic fatty liver disease, cirrhosis, and hepatitis B and C are more strongly associated with iCCA [5] whereas bile duct conditions and sclerosing cholangitis correlate more closely with eCCA. Gallstones, chronic gallbladder infection, porcelain gallbladder, an unusual sign of chronic cholecystitis, Mirizzi's syndrome, Salmonella infections, high consumption of fried foods, and exposure to toxins and heavy metals predispose a person to GBC [1].

This guideline is based on a systematic review of relevant published studies and with the consensus of ten treatment expert oncologists from GEMCAD (Spanish Multidisciplinary Group of Digestive Cancer), TTD (Digestive Tumor Treatment Group) and SEOM (Spanish Society of Medical Oncology). The Infectious Diseases Society of America-US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines has been used to assign levels of evidence and grades of recommendation.

The most usual symptoms of BTC are the appearance of jaundice, especially in CCA or AoVC, due to biliary tract obstruction. This is less common in the case of GBC. If the tumor is diagnosed in an advanced stage (once it has metastasized), the patient may report a loss of appetite and weight without apparent cause. Abdominal pain can be another symptom that may prompt us to suspect bile duct cancer, although it is a common symptom of many diseases [7].

The diagnosis of BTC can be challenging. A preoperative biopsy is not always required prior to proceeding with a definitive curative resection. Nevertheless, pathologic diagnosis for histologic classification and NGS, with core needle biopsy sample when feasible, is mandatory for all patients undergoing systemic chemotherapy.

Imaging is mandatory to make a differential diagnosis and confirm the anatomical location of BTC, assess its extension, and draw up a treatment plan. The degree of biliary obstruction; hepatic, vascular, and lymph node invasion, and the presence of metastases must be determined.

Recommended initial explorations are detailed in Table 1 . Liver function should be analyzed by means of blood tests and the presence of any underlying liver or biliary tract disease, including HBV and HCV infection, risk factors for non-alcoholic liver disease, or autoimmune diseases, such as sclerosing cholangitis or primary biliary cholangitis should be explored. Table 1 Diagnostic and staging in BTC

Serum carbohydrate antigen (CA 19.9) is a nonspecific marker that may be increased in BTC. When elevated, it is a prognostic marker and can be beneficial when evaluating treatment response [7].

Endoscopic ultrasonography (EUS) ± biopsy can be used to gauge locoregional extension of pCCA, eCCA and GBC [8 , 9]; likewise, percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP) may be performed to relieve biliary obstruction.

For all BTC, thoraco-abdomino-pelvic computed tomography (CT) is needed to determine the extent of primary disease and probe for metastases [10].

MRI is the benchmark to establish local extension of pCCA and eCCA, including biliary tract and vascular anatomy, and to identify hepatic metastases.

As for [18F]–2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), it is less sensitive in cases of infiltrating vs. mass-forming CCA. Its positive predictive value is poor in sclerosing cholangitis, biliary prosthesis, or granulomatous disease. It is not recommended for primary diagnosis but may detect nodal metastases, distant metastases, and disease recurrence [11].

Staging is performed according to the Union for International Cancer Control (UICC) TNM (tumor-node-metastasis) staging manual (8 th edition) and is specific for every subtype of BTC [12]. pCCA are further subclassified as per the Bismuth-Corlette classification to describe anatomic location [7 , 13]. (See Table 2). Table 2 Bismuth–Corlette classification of pCCA (perihilar CCA)

Thoraco-abdomino-pelvic CT remains the gold standard to ascertain lymph node and metastatic extension (III, A), while MRI is the reference imaging study for local extension of pCCA and eCCA and to discover hepatic metastases (III, A). FDG-PET is not recommended for primary diagnoses, but may facilitate detection of nodal metastases, distant metastases, and disease recurrence (III, C). Staging is determined based on according to the 8 th edition of the UICC staging manual and is specific to every subtype of BTC. pCCA are further subclassified according to the Bismuth-Corlette classification to describe their anatomical location (III, A). When feasible, pathologic diagnosis with a core needle biopsy sample is mandatory for histologic classification and NGS analysis.

BTC are primarily adenocarcinomas that arise from the epithelial cells lining the bile ducts. Histologically, these tumors are characterized by glandular structures that may exhibit varying degrees of differentiation, ranging from well-differentiated tumors with clear glandular architecture to poorly differentiated tumors with solid sheets of cells. The presence of a dense desmoplastic stroma, which is a hallmark of these cancers, can make the tumors difficult to distinguish from benign conditions, requiring further study [14 , 15].

iCCA exhibits 3 growth patterns: mass-forming (78% of cases), which are large lesions in the liver parenchyma with possible necrosis or mucin production; periductal infiltrating (16%), characterized by infiltration along bile ducts, and intraductal growing (6%), featuring polypoidal growth within bile

ducts. Perihilar and distal cholangiocarcinoma typically appear as either periductal infiltrating (73%) or intraductal papillary (27%) [14]. Precursor lesions include biliary intraepithelial neoplasia and intraductal papillary neoplasms of the bile duct (IPNB), though their connection to specific cancer types remains controversial. No precursor has been identified for mass-forming iCCA.

Immunohistochemistry (IHC) plays a crucial role in the differential diagnosis, with markers such as CK7, CK19, and CA19 - 9 being commonly used to confirm the biliary origin of the tumor. In addition, HER2/neu overexpression is of clinical interest as it can inform targeted therapy, given that HER2-targeted treatments are available [7 , 14 – 17].

With sample scarcity in mind, perform rational histopathological evaluation to confirm the diagnosis of BTC, utilizing IHC markers such as CK7, CK19, and CA19 - 9 to verify biliary origin. [III, B] Assess iCCA for growth patterns (mass-forming, periductal infiltrating, and intraductal growing) as these have both diagnostic and prognostic implications. [III, B].

Approximately 45% of all BTC patients harbor potentially targetable molecular alterations [7 , 15 – 17]. In recent years, molecular profiling through next-generation sequencing (NGS) has become the cornerstone of BTC management. Current guidelines recommend comprehensive molecular profiling and investigation of microsatellite instability (MSI) and HER2/neu overexpression by IHC in cases with metastasis [7 , 16 , 18]. This approach enables key genetic alterations to be identified that provide mostly predictive information for targeted therapies. (See Table 3). Table 3 Key molecular markers in BTC

The incidence of molecular alterations may vary according to anatomic location (Fig. 1) [16 , 17]. Fibroblast growth factor receptor 2 (FGFR2) fusions are particularly notable among these alterations, occurring in approximately 10–15% of iCCA [19]. IDH1 and IDH2 mutations represent another important target, found in 10–25% of iCCA cases [20]. These mutations result in the production of an oncometabolite that contributes to tumorigenesis. KRAS mutations, present in approximately 15–25% of BTC, are generally associated with a poor prognosis. [7 , 16]. NTRK fusions are infrequent (< 1%), but identifying these alterations is critical as they present a clear target for effective treatment [15 , 17]. HER2/neu amplification or overexpression, observed in 5–20% of gallbladder cancers and a smaller percentage of other BTC, is another actionable alteration [21]. MSI and high tumor mutational burden (TMB) are found in a small subset of BTC (~ 1–5%) and predict a favorable response to immune checkpoint inhibitors [7 , 16 , 17]. Fig. 1 Anatomic distribution of potentially actionable molecular alterations in BTC (dCCA or eCCA: extrahepatic cholangiocarcinoma)

Comprehensive molecular profiling using NGS should be performed to identify potential targetable alterations (e.g., IDH1/2 mutations, FGFR2 fusions, KRAS mutations, BRAF V600E mutations, NTRK fusions) in BTC, focusing on metastatic cases. [II, A] Test for HER2/neu overexpression. [II, A] Include MSI testing as part of BTC molecular profiling to determine candidates for immunotherapy. [II,B] NGS analysis must be carried out at diagnosis or as early as possible in the course of the disease.

TNM classification (Tables 4 , 5 , 6 , 7 , 8) varies depending on location: Intrahepatic (iCCA) (Table 4).

Perihilar (pCCA): From biliary proximal bifurcation to the cystic duct. (Table 5).

Distal extrahepatic (eCCA): Between cystic duct entry and the end of the common bile duct. A minimum of 12 lymph nodes are needed for staging (Table 6).

Ampullary (AoVC): Confluence of the distal common bile and the main pancreatic duct in the duodenum. Carcinoma can be intra-ampullary (biliary ducts) or periampullary (from duodenum or pancreas). Classification into intestinal or pancreatobiliary subtype is necessary t. A minimum of 12

lymph nodes is recommended (Table 7).

Gallbladder (GBC). A minimum of 6 lymph nodes are recommended (Table 8).

T1a- Solitary, < 5 cms without vascular invasion

T1b- Solitary > 5 cms without vascular invasion

Multiple (with or without vascular invasion)

T4.—Involving local extrahepatic structures by direct invasion

Tis.- Carcinoma in situ/high-grade dysplasia

T1.- Confined to the bile duct, with extension up to the muscle layer or fibrous tissue

T2a.- Invades beyond the bile duct to surrounding adipose tissue

T2b.- Invades adjacent hepatic parenchyma

T3.- Invades unilateral branches of the portal vein or hepatic artery

T4.- Invades the main portal vein or its branches bilaterally, or common hepatic artery, or second-order biliary radicals with contralateral portal vein or hepatic artery involvement

N1.- Metastasis to 1–3 regional lymph nodes

N2.- Metastasis to > 4 regional nodes

Distal extrahepatic bile ducts carcinoma

Tis.- Carcinoma in situ/high-grade dysplasia

T1.- Invades the bile duct wall < 5 mms

T4.- Involves the celiac axis, mesenteric, and/or hepatic artery

N1.- Metastasis to 1–3 regional lymph nodes

N2.- Metastasis to > 4 regional nodes

T1a.- Limited to the ampulla of Vater or sphincter of Oddi

T1b.- Invades beyond the sphincter of Oddi and/or into the duodenal submucosa

T2.- Invades into the muscularis propria of the duodenum

T3b.- Invades the pancreas > 0.5 cm or peripancreatic/periduodenal tissue or duodenal serosa

T4.- Involves the celiac axis, and mesenteric and/or common hepatic artery

N1.- Metastasis to 1–3 regional lymph nodes

N2.- Metastasis to > 4 regional nodes

T2a.- Invades perimuscular connective tissue on the peritoneal side

T2b.- Invades the perimuscular connective tissue on the hepatic side

T3.- Perforates the serosa and/or invades the liver and/or one other adjacent organ or structure

T4.- Invades main portal vein or hepatic artery or > 2 extrahepatic organs or structures

N1.- Metastasis to 1–3 regional lymph nodes

N2.- Metastasis to > 4 regional nodes

Tables 4 , 5 , 6 , 7 , 8 . BTC Staging (8 TH Edition AJCC/TNM) according to primary tumor location [22].

The main prognostic factor in CCA is TNM Staging; however, high tumor grade, multiple lesions, margin involved following surgery, lymph node metastasis, vascular and perineural invasion, high serum bilirubin, and perioperative transfusion were associated with survival [23 , 24]. The primary tumor location and number of metastatic sites also correlate with survival. Lower stages at diagnosis are more common in AoVC, followed by pCCA, eCCA, GBC, and iCCA. Five year survival rates were as follows: AoVC, 48.5%; GBC, 28.5%; pCCA and eCCA, 19.9%, and iCCA, 10.8% [25]. eCCA exhibits better prognosis than pCCA [26]. Other prognostic factors include performance status, serum lactate dehydrogenase (LDH), neutrophil-to-lymphocyte ratio, older age, Ca 19.9 levels, and other serum markers [27 , 28].

There are two iCCA types: Large duct (central location) responds less well to chemotherapy and entails worse prognosis. It is associated with perineural infiltration, higher TMB, CA 19.9, worse stage at diagnosis, mucin-producing, and often expresses TP53 (10–40%) and KRAS mutations (15–30%) [29]. Small-duct iCCA (peripheral location) respond better to chemotherapy, rarely produce mucin, and are associated with IDH1/2 mutations (15–20%) and FGFR- 2 fusions (10–20%) [30].

The presence of TP53 , K-RAS mutations (specially G12 V), ARID 1 A , MET and BRAF mutations, high programmed cell death ligand (PDL1), variants in ERBB2/3/4, BRCA- 1 , MUC, and p27 have also been associated with poor prognosis [28 , 30 – 32]. In contrast, FGFR alterations point toward better survival [30].

The most important predictive factors are targetable genetic alterations, present in up to 40% of BTC [30]. In iCCA, FGFR2 fusions and IDH1 mutations predict survival benefits with their specific inhibitors [7 , 33]. HER2/neu overexpression, amplification, or activating mutations also has a good response with anti-HER2 drugs and better survival [33]. Other less common targetable alterations are BRAF V600E, NTRK, MET amplification, ALK, RET or ROS fusions, and KRASG12 C mutation, all of which yield benefit after targeted therapy [7 , 30 , 33].

High-TMB tumors respond better to immunotherapy, but no correlation has been proven with PDL1 [30 , 34]. MSI-high or mismatch repair deficiency (dMMR) are predictive of a greater, lasting response to immunotherapy [35]. Other series have reported up to 16% of alterations in DNA repair genes (MLH- 1, MSH- 2, MSH- 6, BAP1, ATM, BRCA1 , and BRCA2) of ICC and 45% of ECC [36].

Surgical resection with free margins is currently the only curative treatment for BTC, but only 20–30% of all cases are candidates for curative surgery. The nature of surgery should be agreed

upon by a specialized multidisciplinary team (MDT). Despite improvements in patient selection and surgical techniques, the risk of relapse remains high.

Since 2017, five randomized trials have explored different chemotherapy (CT) regimens as adjuvant treatment: Two of these studies explored the role of gemcitabine-based adjuvant therapy. The BCAT study [37] randomized 226 patients with eCCA to gemcitabine vs. observation, while and the PRODIGE- 12 trial [38] included 196 patients with CCA and GBC and evaluated the efficacy of gemcitabine-oxaliplatin vs. observation. Both studies failed to demonstrate a significant survival benefit with chemotherapy.

The phase III BILCAP trial randomized 447 patients with CCA and GBC to eight cycles of capecitabine vs. observation, starting within 16 weeks of surgery. At a median follow-up of 106 months, the study did not meet its primary endpoint in the intention-to-treat (ITT) population, with a median overall survival (OS) of 49.6 months with capecitabine vs. 36.1 months with observation (HR 0.84; 95% CI, 0.67–1.06). However, OS improved significantly in the pre-specified ITT sensitivity analysis (adjusted for minimization factors, nodal status, grade, and sex) (HR 0.74; 95% CI, 0.59–0.94) and in the per-protocol population, with a median OS of 52.3 months for capecitabine and 36.1 months for observation (HR 0.79) (0.63–1.00) [39]. Based on these results, adjuvant capecitabine is currently considered the standard of care.

The phase III ASCOT trial [40] compared four cycles of S- 1 vs. observation in 440 patients with resected BTC, including AoVC. Updated efficacy confirmed the survival benefit of S- 1 (5-year OS 64.1% for S- 1 and 52.2% for observation) (HR 0.723; 95% CI, 0.551–0.948; $p = 0.0187$). S- 1 is included as an adjuvant option in Asian guidelines.

The randomized phase II STAMP trial demonstrated no survival benefit with the combination of cisplatin–gemcitabine vs. capecitabine in subjects with lymph node-positive eCCA [41] The ongoing phase III ACTICCA- 1 trial is assessing the efficacy of cisplatin–gemcitabine in all BTC subtypes and may further reveal the comparative role of this combination over capecitabine.

No prospective randomized trials have proven any benefit of adjuvant radiotherapy (RT). Small trials and meta-analyses have suggested a survival benefit in individuals at increased risk of recurrence. The phase II SWOG-S0809 trial evaluated adjuvant gemcitabine–capecitabine followed by chemoradiotherapy with capecitabine in 79 patients with resected eCCA or GBC, with good survival rates [42].

Despite the potential benefits, the neoadjuvant approach to treating BTC is currently regarded as experimental.

In the absence of specific randomized trials, systemic treatment should be deemed the initial treatment of choice in the context of a MDT discussion.

Locoregional therapies including ablation, RT, and intra-arterial therapies (hepatic arterial infusion of CT, transarterial chemoembolization, and radioembolization) have proven to be safe and effective in small studies, and might be contemplated in selected patients who are not candidates for surgery or to downstage for other treatments. Prospective phase II studies with intra-arterial therapies in combination with CT show promising subjects in patients with liver-limited iCCA [43].

In case of response after locoregional or systemic treatment, patients should be re-evaluated by the MDT to discuss surgery.

Systemic therapy is the standard therapy for locally advanced disease. Although still a field of evolution, it is widely accepted that patients with unresectable hilar cholangiocarcinoma without lymph node involvement should be considered for orthotopic liver transplantatation (OLT), and referred to a specialized center. Patients with intrahepatic cholangiocarcinoma ≤ 3 cm in the

context of cirrhotic liver disease maybe considered for OLT, but also for locoregional therapies, always after systemic therapy and tumour control.

MDT discussion should be the forum for all agreed treatment decisions. [III, A].

Adjuvant CT with eight cycles of capecitabine should be offered to post-resection BTC patients [II, A].

Following completion of adjuvant capecitabine, RT could be considered as an exception in selected cases (R1 resection of GBC or eCCA) [III, C].

In the event of response after locoregional or systemic treatment of locally advanced tumors, patients should be re-assessed by the MDT for surgery [IV, B] (See Fig. 2). Fig. 2 Algorithm of management for localized and locally advanced BTC

Treatment for advanced BTC relies on the backbone of chemotherapy, to which immunotherapy has recently been incorporated. Cisplatin and gemcitabine (CisGem) became the standard chemotherapy option following data from the ABC- 02 clinical trial, which compared this schedule to single agent gemcitabine [44]. The addition of cisplatin to gemcitabine alone in this trial improved both overall survival (OS) [HR (Hazard ratio) 0.64 (95% CI 0.52–0.80)] and progression-free survival (PFS) [HR 0.63 (95% CI 0.51–0.77)] achieving median OS and PFS of 11.7 and 8.0 months, respectively. For patients who have a contraindication for cisplatin, gemcitabine alone [1] or gemcitabine combined with oxaliplatin [45] can be considered as alternatives.

Recently, the addition of checkpoint inhibitors such as durvalumab and pembrolizumab combined with CisGem are considered standard of care first line setting in the absence of contraindications to immunotherapy. This is based on the TOPAZ- 1 [46 , 47] and KEYNOTE- 966 [48] studies, two randomized phase III clinical trials exploring the combination of immune-checkpoint inhibitors (durvalumab and pembrolizumab, respectively) with chemotherapy (CisGem) over CisGem combined with placebo. Overall, both studies exhibit an improvement in OS [TOPAZ- 1: HR 0.76 (95% CI 0.64–0.91); KEYNOTE- 966: HR 0.83 (95% CI 0.72–0.95)]. PFS [TOPAZ- 1: HR 0.75 (95% CI 0.63–0.89); KEYNOTE- 966: HR 0.86 (95% CI 0.75–1.00)] and response rate improvement (TOPAZ- 1: 18.7% (CisGem) vs. 26.7% (CisGem + durvalumab); KEYNOTE- 966: 29% in both arms) has only been confirmed in the TOPAZ- 1 trial with durvalumab.

Long-term follow-up, of up to 36 months, has also been reported [48 , 49] with a clinically relevant impact in favor of the checkpoint inhibitor arm in both studies (36-month survival rate: TOPAZ- 1: 6.9% [CisGem) vs. 14.6% (CisGem + durvalumab); KEYNOTE- 966: 11% (CisGem) vs. 13% (CisGem + pembrolizumab)]. Interestingly, the benefit of checkpoint inhibitors is independent of PD-L1 expression and of the presence of other targetable alterations [50] such that all cases appear to benefit equally from this approach.

For locally advanced unresectable and metastatic disease, cisplatin and gemcitabine combined with immune-checkpoint inhibitors (durvalumab [I, A] or pembrolizumab [I, A]) is considered the standard of care. In the presence of contraindications to immunotherapy cisplatin and gemcitabine alone can be contemplated. [I, A] If any contraindications to cisplatin, gemcitabine in monotherapy, or gemcitabine with oxaliplatin are alternatives to factor into the decision. [II, A] (Fig. 3).

After progression to a first line regimen, around 45% [51] of all BTC patients are fit enough to attempt a second line. The combination of oxaliplatin and 5 FU/LV (FOLFOX regimen) is deemed the standard of care, according to the results of the ABC06 trial. In this phase III study, 162 patients with advanced BTC in progression to a first line treatment of CisGem, were openly randomized 1:1 to receive FOLFOX vs. active supportive care [52]. The study yielded positive results for OS [mOS 6.2 vs. 5.3 m, respectively (HR 0.69; p = 0.031), with a 12-m OS-rate of 25.9% vs. 11.4%)] the toxicity profile was manageable. There are not predictive factors for this regimen (Fig. 3).

Liposomal irinotecan (Naliri) with 5 FU/LV demonstrated superiority over 5 FU/LV in a Korean phase II randomized trial (NIFTY) [53]. However, this benefit was not replicated in the NALIRICC, a German clinical trial with a very similar design. We therefore do not recommend using this regimen outside the context of a clinical trial [12]. The XELIRI regimen (capecitabine and irinotecan) was tested in a randomized Phase II trial and demonstrated greater PFS with respect to irinotecan in monotherapy [54]. Nevertheless, given its toxicity profile, we do not recommend that it be used routinely. Based on the control arm of these trials, fluoropyrimidines in monotherapy (5 FU/LV or capecitabine) or with traditional irinotecan can be an alternative approach for those individuals unable to receive a doublet regimen, such as those with significant cumulative neurotoxicity [55].

Alternative FOLFIRI with traditional irinotecan is often used in clinical practice. It displayed a different safety profile with less peripheral neuropathy and thrombocytopenia in a Korean randomized phase II trial compared to FOLFOX [56]. However, FOLFIRI failed to exhibit efficacy superiority over FOLFOX (mOS 6.3 m vs. 5.7 m, respectively; HR 1.1; p = 0.683). In highly selected cases, such as those with very good PS and for whom platin salts are contraindicated, combination therapy with FOLFIRI may be a reasonable alternative. Toxicity profile and lack of evidence of improved overall survival must be factors to be taken into account.

Molecular testing has become mandatory in subjects with BTC and results should be available prior to initiating the second line treatment [56]. The list of actionable alterations in advanced BTC is rapidly growing. IDH1 (R132X), FGFR2 (fusion/rearrangements), HER2/neu (amplification/overexpression), BRAF (V600E), and MSI-H (or dMMR) should be always included.

Ivosidenib, an oral IDH1 inhibitor, is indicated for advanced and refractory cholangiocarcinoma with IDH1 mutation (10–20% of patients with iCCA) as per the results of the ClarIDHy trial. This was a phased III randomized (2:1) double-blinded trial that demonstrated longer PFS with this drug vs. placebo in 185 people with IDH1 m CCA previously treated with up to two treatment regimens (median PFS 2.7 vs. 1.4 months; HR 0.37) and an excellent safety profile [20].

Pemigatinib or futibatinib are small molecules that inhibit the fibroblast growth factor receptor (FGFR) indicated in cases of refractory FGFR2f/r CCA, in keeping with the results of their respective non-randomized single-arm phase II trials (FIGHT- 202 and FOENIX-CCA2) that exhibited an unprecedented overall response rate (23.1% and 42%, respectively). Hyperphosphatemia and nail and retinal toxicity must be addressed [19 , 57].

Dabrafenib–Trametinib, an oral doublet of BRAF/MEK inhibitors has received the agnostic approval of the FDA since the publication of the ROAR basket study [58]. Likewise, it is recommended for advanced BTC and V600E BRAF (5% of patients with CCA) inasmuch as the cohort in this study showed an ORR of 51% (OS 14 m).

The combination of trastuzumab–pertuzumab is an option for advanced and refractory BTC in cases with HER2/neu overexpression/amplification or both (5%– 10% of all CCA and up to 20% of GBC) based on the results of a non-randomized phase II study (MyPathway) [59]. This trial revealed positive results compared to historical controls (ORR 23%; PFS 10.9 m). Trastuzumab-Deruxtecan (antibody drug conjugate) has recently been approved by the FDA in light of the results of Destiny-PanTumor02 that achieved an ORR 56.3% in the cohort of HER2 + advanced BTC (IHQ 3 +) [60]. Zanidatamab, a bispecific antiHER2 antibody, has become a new option in the same setting (HER2 amplification and 3 +) after the results of the HERIZON-BTC01 trial (ORR 41%)[61].

Pembrolizumab is an aPD1 monoclonal antibody with agnostic approval for MSI-H/dMMR advanced refractory tumors. The BTC cohort in the pivotal KN158 basket trial yielded a 41% ORR [62].

While very rare in BTC, certain molecular alterations with their respective targeted therapies have received agnostic approvals. Such is the case with NTRK and RET fusions/rearrangement or the presence of high TMB (TMB > 10 mutations/Mb) with entrectinib/larotrectinib, selpercatinib [63 – 65] and pembrolizumab, respectively. They can be used when they are detected in a somatic molecular panel of advanced BTC.

We suggest rechecking the NGS panel regularly for molecular alterations labeled as non-targetable, in search of changes in status, not only for approved drugs but also for opportunities to participate in clinical trials.

With respect to therapy beyond first line: ivosidenib is recommended to treat individuals with CCA and IDH1 mutations who have progressed after ≥ 1 prior line of systemic therapy. [I, A] FGFR inhibitors (pemigatinib and futibatinib) are recommended in cases of patients with FGFR2 fusions who have progressed after ≥ 1 prior line of systemic therapy. [III, A] Dabrafenib-trametinib is recommended for subjects with BRAFV600E mutations who have progressed after ≥ 1 prior line of systemic therapy. [III, A] Pembrolizumab is recommended in patients with MSI-H/dMMR who have progressed on or are intolerant to prior non-immune checkpoint inhibitor-containing treatment [III, A] or the presence of high TMB (TMB> 10 mutations/Mb). [IV, A] NTRK inhibitors (entrectinib/larotrectinib) are recommended in people with NTRK fusions who have progressed on or are intolerant to prior treatment. [III, A] HER2-directed therapies (trastuzumab–pertuzumab, trastuzumab-deruxtecan, zanidatamab) can be contemplated for patients with HER2/neu overexpression/amplification who have progressed on or are intolerant to prior treatment. [III, A] Selpercatinib can be considered for individuals with RET fusions who have progressed on or are intolerant to prior treatment. [III; A] (Fig. 3).

As yet there is insufficient data for specific follow-up in BTC following curative treatment; similarly there is no evidence that indicates that regular follow-up has any significant impact on outcomes. Nonetheless, based on the high risk of recurrence during the first 2 years post-curative treatment, we recommend three to six monthly visits during the first two years after therapy, including clinical examination, laboratory test, tumor markers (CEA, CA 19–9), and CT of the thorax, abdomen, and pelvis. These visits can transition to annual appointments until five years of follow-up [7] [IV, B].

The most frequent long-term complications of BTC after different types of surgery are malabsorption (80%), with nutritional deficits or diarrhea (30%), due to insufficiency of the residual pancreas, with a significant impact on quality of life and, therefore calls for individual chronic treatment. Other complications include biliary obstruction that requires a specialized multidisciplinary team to determine the optimal approach to drainage [IV, A].

Patients with recurrence or advanced stages who are treated with systemic agents are evaluated clinically and for tumor progression by CT every three months in order to make treatment decisions [III, A].

Thanks to the success of new therapeutic strategies [66], there is a small cohort of BTC survivors and a new approach to follow-up and prevention for long-term toxicity and management should be elaborated. A MDT dedicated to meeting the specific support needs of long-term survivors should be considered.

Despite the fact that there is no universal follow-up schedule, follow-up is suggested for patients with resected BTC, although there is insufficient evidence that points toward an impact on overall survival. [IV, B] Biliary obstruction requires a specialized MDT to determine the optimal approach to drainage. [IV, A] A MDT should follow up long-term survivors [V, A].

Thoraco-abdominal-pelvic CT remains the reference examination for lymph node and metastatic spread. [III, A] MRI is the gold standard to assess local extension of pCCA and eCCA and to detect hepatic metastases. (III, A) FDG-PET is not recommended for primary diagnosis, but might make to

possible to identify nodal metastases, distant metastases, and disease recurrence. (III, C) Staging is conducted as per the 8th edition of the AJCC/UICC staging manual and is specific for each BTC subtype. pCCA are further subclassified according to the Bismuth-Corlette classification to describe their anatomical location (III, A).

Bearing in mind sample scarcity, rational histopathological evaluation should be performed to confirm the diagnosis of BTC, utilizing IHC markers such as CK7, CK19, and CA19 - 9 to verify biliary origin. [III, B] iCCA growth patterns (i.e., mass-forming, periductal-infiltrating, and intraductal-growing) should be assessed, inasmuch as they entail diagnostic and prognostic implications (III, B).

Comprehensive molecular profiling should be conducted using NGS to identify potential targetable alterations (e.g., mutations in IDH1/2, FGFR2 fusions, KRAS, BRAF V600E mutations, and NTRK fusions) in BTC, focusing on advanced cases (II, A). Subjects should be tested for HER2/neu overexpression. (II, A); MSI testing should be included as part of BTC molecular profiling to identify candidates for immunotherapy (II, B).

Eight cycles of adjuvant CT with capecitabine should be offered to individuals with BTC following resection. [II, A] RT, after completing adjuvant capecitabine, could be considered in selected patients (R1 resection of GBC or eCCA). (III, C) In cases in which there is response after locoregional or systemic treatment of locally advanced tumors, patients should be re-evaluated by the MDT to consider surgery [IV, B] (See Fig. 2).

For locally advanced unresectable and metastatic disease, combination of cisplatin and gemcitabine with immune-checkpoint inhibitors (durvalumab [I, A] or pembrolizumab [I, A]) is considered the standard of care. In the presence of contraindications to immunotherapy or cisplatin, gemcitabine in monotherapy might be considered. [I, A] or combination with oxaliplatin are alternatives to take into account [II, A] (See Fig. 3).

The combination of oxaliplatin and 5 FU/LV (FOLFOX regimen) is regarded as the standard of care in the second line setting in patients without targetable alterations. (I, A) Monotherapy with fluoropyrimidines (5 FU/LV or capecitabine) or with traditional irinotecan can be an alternative approach for individuals unable to receive a doublet regimen. [II, B] In highly selected cases, combination therapy with FOLFIRI may be a reasonable option [II, C] (See Fig. 3).

Targeted therapy beyond first line: ivosidenib is recommended in patients with CCA and IDH1 mutations who have progressed after ≥ 1 prior line of systemic therapy. [I, A] FGFR inhibitors (pemigatinib and futibatinib) are recommended in individuals with FGFR2 fusions who have progressed after ≥ 1 prior line of systemic therapy. [III, A] Dabrafenib-trametinib is recommended when there are BRAFV600E mutations in patients who have progressed after ≥ 1 prior line of systemic therapy. [III, A] Pembrolizumab is recommended in subjects with MSI-H/dMMR who have progressed on or are intolerant to prior non-immune checkpoint inhibitor-containing treatment (III, A) or the presence of high TMB (TMB > 10 mutations/Mb). [IV, A] NTRK inhibitors (entrectinib/larotrectinib) are recommended in people with NTRK fusions who have progressed on or are intolerant to prior treatment. [III, A] HER2-directed therapies (trastuzumab–pertuzumab, trastuzumab-deruxtecan, zanidatamab) can be contemplated in patients with HER2/neu overexpression/amplification who have progressed on or are intolerant to prior treatment. [III, A] Selpercatinib can be considered in patients with RET fusions who have progressed on or are intolerant to prior treatment [III; A] (See Fig. 3).

Participation in clinical trials may be considered as an option in BTC

While there is no universal follow-up schedule, follow-up is suggested for patients with resected BTC, albeit there is insufficient evidence of an impact on overall survival. [IV, B] Biliary obstruction must be addressed by a specialized MDT to determine the optimal approach to drainage. [IV, A] A

MDT should follow up long-term survivors [V, A].

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Compliance with ethical standards. The current study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.