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Short title; Adjuvant treatment in Biliary Tract Cancer

Abstract

Biliary tract cancer, including cholangiocarcinoma (CCA) and gallbladder cancer (GBC) are rare tumours with a rising incidence. Prognosis is poor, since most patients are diagnosed with advanced disease. Only ~20% of patients are diagnosed with early-stage disease, suitable for curative surgery. Despite surgery performed with potentially-curative intent, relapse rates are high, with around 60-70% of patients expected to have disease recurrence. Most relapses occur in the form of distant metastases, with a predominance of liver spread. In view of high tumour recurrence, adjuvant strategies have been explored for many years, in the form of radiotherapy, chemo-radiotherapy and chemotherapy. Historically, few randomised trials were available, including a variety of additional tumours (e.g. pancreatic and ampullary tumours) and most evidence relied on phase II and retrospective studies, with no high-quality evidence available to define the real benefit derived from adjuvant strategies.

Since 2017, three randomised phase III clinical trials have been reported; all recruited patients with resected biliary tract cancer (CCA and GBC) who were randomised to observation alone, or chemotherapy in the form of gemcitabine (BCAT study; included patients diagnosed with extrahepatic CCA only), gemcitabine and oxaliplatin (PRODIGE-12/ACCORD-18; included patients diagnosed with CCA and GBC) or capecitabine (BILCAP; included patients diagnosed with CCA and GBC). While gemcitabine-based chemotherapy failed to show an impact on patient outcome (relapse-free survival (RFS) or overall survival (OS)), the BILCAP study showed a benefit from adjuvant capecitabine in terms of OS (pre-planned sensitivity analysis in the intention-to-treat population and in the per-protocol analysis), with confirmed benefit in terms of RFS. Based on the BILCAP trial, international guidelines recommend adjuvant capecitabine for a period of six months following potentially curative resection of CCA as the current standard of care for resected CCA and GBC. However, BILCAP failed to show OS benefit in the intention-to-treat (non-sensitivity analysis) population (primary end-point), and this finding, as well as some inconsistencies between studies has been criticised and has led to confusion in the biliary tract cancer medical community.

This review summarises the adjuvant field in biliary tract cancer, with evidence before and after 2017, and comparison between the latest randomised phase III studies. Potential explanations are presented for differential findings, and future steps are explored.

Introduction

The term “biliary tract cancer” (BTC) includes tumours of the gallbladder (GBC), cholangiocarcinoma (CCA) and ampullary tumours. Cholangiocarcinomas are subdivided according to location into intrahepatic cholangiocarcinoma (iCCA) and extrahepatic cholangiocarcinoma (eCCA) [eCCA are further divided in hilar cholangiocarcinoma (hCCA) and distal cholangiocarcinoma (dCCA)].

Although BTCs account for only 0.7% of all malignant tumours and 3% of all gastrointestinal malignancies in adults, both incidence and mortality are increasing, predominantly due to a rise in iCCA (1-3). BTCs are characterised by poor prognosis, with a 5-year survival of around 5-15% when all stages are analysed jointly (4, 5).

There is an urgent need to improve outcomes for patients diagnosed with BTC (6), and three main potentially actionable areas are suggested.

First, strategies for early detection are required, since the majority of patients (around 70%) are diagnosed with advanced-stage disease (not suitable for curative surgery) (7, 8). Identification of new diagnostic biomarkers, and definition of populations at risk for development of screening strategies, are areas to explore (9, 10).

Secondly, for patients suitable for resection, the relapse rate following surgery remains high (11, 12). Even though the 5-year survival rate is slowly, but steadily increasing, for CCA and GBC (**Figure 1**), there is room for further improvement and effort is required not only in the identification of risk factors, but also in the development of new adjuvant strategies.

Thirdly, new strategies for management of advanced disease are urgently needed (79). For many years, cisplatin and gemcitabine has been the standard of care first-line chemotherapy schedule for patients with inoperable disease (80, 81). Triple-chemotherapy combinations are also being explored with promising results in the first-line setting (82, 83) and the combination of oxaliplatin and 5-fluorouracil (FOLFOX) has been recently established as a new second-line strategy (84). Development of new agents (85), liver-directed therapies (86-89), external beam radiotherapy (90) and targeted therapies, with inhibition of fibroblast growth factor receptor (FGFR) fusion rearrangements and isocitrate dehydrogenase (IDH)-1 and -2 mutations (91) are rapidly changing the treatment paradigm in metastatic disease (92, 93).

Until recently, the evidence supporting the role of adjuvant chemotherapy in CCA and GBC was scarce and adjuvant therapy was not considered standard practice in many countries (13). Since 2017, data from phase III randomised studies have been reported and have challenged the role of adjuvant

therapy in resected BTC (65, 77, 78). Even though interpretation of the outcomes of these studies, specifically due to discrepant findings, has not been straight forward (94), current practice has changed based on these results (95). This review summarises and provides an overview of the latest data in the field of adjuvant therapy in CCA and GBC.

Patterns of relapse

Despite potentially curative surgery, frequent relapse is the rule for CCA and GBC (13). There is a predominance for distant metastases for GBC (65, 96), while reported relapse patterns vary between studies for CCA, with some studies supporting a predominance of distant (liver) metastases (65), while others report a higher rate of loco-regional relapse (96). The fact that distant metastases seem to be predominant over local recurrence supports the use of systemic chemotherapy strategies in the adjuvant setting for GBC and CCA. However, radiotherapy is still an option for patients with R1 (microscopically-involved resection margins) disease due to risk of local recurrence; even though level of evidence is low (95).

Factors associated with poor outcome

Some of the factors associated with increased risk of relapse include the presence of R1, high serum carbohydrate antigen (CA) 19-9 and the presence of lymph node metastases (5, 55, 97-105). Some evidence does also support that patients with eCCA have increased risk of tumour recurrence (77).

In a recent series of patients with resected eCCA, the presence of post-operative CA19-9 (Hazard Ratio (HR) 2.26) and presence of lymph node infiltration (HR 2.33) were associated with worse outcomes (overall survival (OS)). Patients with resected eCCA with high pre-and post-operative CA19-9 were shown to have a higher distant metastasis rate and shorter disease-free interval (55). Involvement of adjacent structures, perineural invasion, and poorly-differentiated histology have also been associated with poor outcomes for resected eCCA (5, 103, 104, 106-110).

Factors associated with increased relapse rate and poor prognosis for resected iCCA include R1, lymphatic invasion, vascular invasion and periductal infiltrating disease (5, 98, 99, 101, 102, 106, 111), while R1-resection, depth of mural invasion, lymph node metastasis, extramural extension and perineural invasion have been proposed for GBC (97, 112-114). Prognostic nomograms have been designed for patients with a resected iCCA (11); this nomogram included serum carcinoembryonic antigen (CEA), CA19-9), tumour diameter and number, vascular invasion, lymph node metastasis, direct invasion, and local extra-hepatic metastasis, and was superior in prognostic discrimination to five other staging systems for iCCA ($p<0.001$).

Adjuvant scenario prior to 2017

Prior to 2017, there was a lack of dedicated randomised studies exploring adjuvant therapy in patients with CCA and GBC (105, 115). The use of adjuvant therapy (both in the form of chemotherapy or chemoradiotherapy) was supported by a meta-analysis published in 2012 by Horgan and colleagues (105). This systematic review and meta-analysis included 20 trials; one randomised study, two Surveillance, Epidemiology, and End Results (SEER) registry studies and 17 retrospective series with a total of 6,712 patients (of whom 1,787 received adjuvant treatment). Of the 20 studies included, 9, 3 and 8 included data on adjuvant radiotherapy alone, chemotherapy alone and chemo-radiotherapy, respectively.

When all studies were included (including SEER registry data), adjuvant treatment did not improve survival in the pooled analysis compared to surgery alone (odds ratio (OR) 0.74, 95%CI 0.55-1.0); moreover, no benefit was identified when gallbladder and cholangiocarcinoma were analysed separately. When the SEER registry data were excluded, there was a benefit in favour of adjuvant treatment in the pooled analysis (OR 0.53, 95%CI 0.39-0.72); with benefit for chemotherapy alone (OR 0.39, 95%CI 0.23-0.66) and for chemo-radiotherapy (OR 0.61, 95%CI 0.38-0.99), while no benefit was shown for radiotherapy alone (OR 0.98, 95%CI 0.67-1.43) (105). Horgan and colleagues analysed the benefit of adjuvant therapy in two high risk populations (R1 and presence of lymph node metastases (N1), and showed a benefit of adjuvant therapy in both groups with OR of 0.36 (95%CI 0.19-0.68) and 0.49 (95%CI 0.30-0.80), respectively.

One of the main criticisms of this meta-analysis was the fact that only one randomised study was available at the time, therefore relying on retrospective (with major risk of selection bias) and small phase II studies employing multiple different chemotherapy schedules. It was clear that further prospective studies to define the benefit of adjuvant treatment were required (13, 116) as adjuvant strategies were used variably worldwide.

Previously available randomised clinical trials exploring the role of adjuvant therapy

Only two randomised studies were available prior to 2017 (14, 117), but none were exclusively dedicated to CCA and GBC and did, instead, include a variety of pancreato-biliary tumours.

The first randomised study by Takada and colleagues in 2002 (14) evaluated adjuvant therapy with mitomycin-C and 5-fluorouracil (MF arm) versus surgery alone (control arm). The study recruited a total of 508 patients with resected pancreato-biliary tumours (including fully-resected CCA (n = 118; 58 in the MF group and 60 in the control group, but including less than half with curative-intent resection) and GBC (n = 112; 69 in the MF group and 43 in the control group). The study showed evidence of benefit for the GBC group only, both in terms of OS (5-year OS rate was 26.0% (MF group)

14.4% (control group); p-value 0.0367) and disease-free survival (RFS) (5-year OS rate was 20.3% (MF group) 11.6% (control group); p-value 0.0210). No benefit was identified for patients with CCA, either in terms of OS (5-year OS rate was 26.7 % (MF group) vs 24.1% (control group); p-value >0.05) or RFS (5-year RFS rate was 20.7% (MF group) vs 15.8% (control group); p-value 0.8892) (14). Based on these findings, there was evidence supporting the role of adjuvant chemotherapy for GBC, even though its role remained unclear for CCA.

The ESPAC-3 trial explored the role of adjuvant chemotherapy for resected pancreato-biliary tumours (117). In this trial, 428 patients with periampullary malignancies (a heterogeneous group including 297 ampullary cancers, 96 bile duct cancers and 35 "other" subtypes) were randomised after curative surgery to observation alone, adjuvant 5-FU or adjuvant gemcitabine chemotherapy. In the 96 patients with CCA, adjuvant chemotherapy did not improve OS (27.2 months (95% CI 15.4-31.9) vs 18.3 months (95% CI 12.9-28.7) vs 19.5 months (95% CI 16.2-36.1) for the observation, 5-FU and gemcitabine groups, respectively) (117).

Other non-randomised studies focused on CCA

The role of adjuvant radiotherapy and chemotherapy has been explored in small phase II and retrospective studies. The available data for adjuvant chemotherapy was based on retrospective studies only (49, 52, 56, 118-122), most of which employed gemcitabine-based regimens with inconsistent findings. Adjuvant radiotherapy, either alone or with radio-sensitising chemotherapy, after resection of CCA had not shown a clear benefit (4) (123-126). Some retrospective and phase II trials appeared to show a benefit compared to surgery alone (119, 127-131), predominantly for incompletely-resected patients. A meta-analysis summarising adjuvant radiotherapy or chemo-radiotherapy studies in eCCA reported that radiotherapy significantly improved OS compared with surgery alone (HR 0.62; 95%CI 0.48-0.78, p<0.001) (132). One of the largest retrospective series exploring the role of adjuvant radiotherapy included a total of 3,839 patients with iCCA from the SEER database (133). The median overall survival was 11 months (95% CI 9-13) for patients treated with surgery followed by adjuvant radiotherapy, versus 6 months (95% CI 5-6) for the group receiving surgery alone; p-value 0.014. Differences were significant when adjusted for other prognostic factors in the multivariable analysis (HR, 0.82 (95% CI, 0.70-0.96)).

Other non-randomised studies focused on GBC

In addition to the randomised phase III study by Takada and colleagues, (14), adjuvant radiotherapy (72, 134-136) and chemo-radiotherapy (45, 69, 74, 137-139) for resected GBC have been explored in multiple phase II and retrospective studies. The largest series was from SEER including 3,187 patients with GBC which showed that adjuvant radiotherapy was associated with improved OS (14 vs. 8

months; p≤0.001) (135). There was also evidence suggesting that those patients with lymph node-positive disease and T2-T3 tumours, appeared to benefit the most from radiotherapy (140) and chemo-radiotherapy (12, 137).

The urgent need for further randomised studies

The two randomised studies available prior to 2017 recruited a wide spectrum of pancreato-biliary malignancies (14, 117), and even though multiple phase II and retrospective studies had been reported, these were heavily influenced by selection bias; and contained a heterogeneous component of radiotherapy and chemotherapy schedules with discrepant findings. Even though some evidence suggested that those patients with poor prognostic factors such as R1 and N1 were the ones deriving the most benefit from adjuvant therapy (105, 141). Therefore, there was an urgent need for dedicated and appropriately powered randomised clinical trials exploring the role of adjuvant strategies following curative resection for patients diagnosed with CCA and GBC (7, 13).

2017-2019: paradigm shift

The era of dedicated randomised trials for patients with CCA and GBC

Three phase III randomised clinical trials were reported and published between 2017 and 2019, all focused on patients with resected BTC (including CCA and GBC) and exploring the role of chemotherapy compared to observation alone after curative surgery (65, 77, 78). **Table 1** and **Figure 2** provide a summary of the design and main findings of these clinical trials.

The BCAT trial randomised patients to gemcitabine (Gem) versus observation alone (65). A total of 226 patients were randomised to Gem (n=117 patients) and observation alone (109 patients; 1 patient was not eligible and therefore excluded from the analysis). Patient demographics were well balanced between study groups. Only patients with eCCA were included in the BCAT trial, including perihilar and distal CCAs only. Around 35.9% (Gem arm) and 33.3% (observation arm) of patients had N1 disease, and the rate of R1-resection was 9.4% in the Gem arm and 13.0% in the observation arm. Chemotherapy was well tolerated, with 52.1% of patients completing the full course of adjuvant Gem. The primary end point was OS; the study identified no significant differences in OS (median 62.3 months (Gem) vs 63.8 months (observation); HR 1.01 (95% CI 0.70-1.45; p-value 0.964). There was no evidence of benefit in RFS (median 36.0 months (Gem) vs 39.9 months (observation arm); HR 0.93 (95% CI 0.66-1.32); p-value 0.693). Based on these findings, the BCAT study failed to show a benefit from Gem chemotherapy in patients with resected eCCA.

The PRODIGE-12/ACCORD-18 trial randomised patients to gemcitabine and oxaliplatin (GemOx) versus observation alone (78). A total of 196 patients were randomised, and 95 and 99 were included

in the intention-to-treat population in the GemOx and the observation arm, respectively. A high proportion of patients included in the PRODIGE-12/ACCORD-18 trial were diagnosed with iCCA (44%) or had N1 disease (36%) and only 13% had R1 resection; these characteristics were balanced between the study arms. The study was powered to identify differences in terms of RFS, with a pre-specified HR of 0.6. The study failed to show a benefit from GemOx chemotherapy in terms of RFS (HR 0.83 (95% CI 0.58-1.19); p-value 0.31); lack of benefit was confirmed in the per-protocol population. There was also no trend towards improved OS (HR 1.08 (95% CI 0.70-1.66; p-value 0.74). Interestingly, most patients with recurrent disease developed presence of distant metastases and were treated with gemcitabine-based chemotherapy. The authors also described a trend towards worse post-relapse survival in the GemOx arm (median OS 8.0 months) versus patients in the observation arm (median OS 15.2 months); HR 1.55 (95% CI 0.98-2.47); p-value 0.06. The median number of chemotherapy cycles delivered were 12, including 10 with oxaliplatin.

The BILCAP trial randomised 447 patients to capecitabine (Cap) (223 patients) and observation alone (224 patients) and recruited patients with both CCA and GBC (77). Within the BILCAP trial, dCCA were the largest subgroup (34% in the Cap arm, 36% in the observation arm), followed by hCCA (29% in the Cap arm, 28% in the observation arm); only 19% in the Cap arm and 18% in the observation arm were iCCA. Regarding prognostic factors, 38% of the patients in each arm were R1 and 48% in the Cap arm and 46% in the observation arm were N1. The BILCAP trial was powered to identify differences in terms of OS in the intention-to-treat (ITT) population adjusted to stratification factors [institution, primary site (iCCA vs hCCA vs dCCA vs GBC), resection margin, and performance status], with a target HR of 0.69. In addition to the OS analysis in the ITT population, the study had pre-planned a sensitivity analysis of OS in the ITT population adjusting the treatment effect for identified prognostic factors and a separate analysis of OS in the per-protocol population. The median OS (ITT population) was 51.1 months (95% CI 34.6-59.1) and 36.4 months (95% CI 29.7-44.5) in the capecitabine and observation arms, respectively. Even though the BILCAP study did not meet its primary end-point in terms of OS in the ITT population (HR 0.81 (95% CI 0.63-1.04); p-value 0.097), adjuvant capecitabine was beneficial, both in terms of OS in the pre-specified ITT sensitivity analysis adjusted for nodal status, grade of disease and gender (HR 0.71 (95% CI 0.55-0.92); p-value 0.010) and in the per protocol population (HR 0.75 (95% CI 0.58-0.97); p-value 0.028). There was also benefit in terms of RFS (median 24.4 months (95% CI 18.6-35.9) and 17.5 months (95% CI 12.0-23.8); HR 0.75 (95% CI 0.58-0.98); p-value 0.033). In the BILCAP study, capecitabine was well tolerated with an expected toxicity profile and no chemotherapy-related death; 55% of the patients who started capecitabine completed the full 8 cycles of adjuvant therapy and 46% required at least one dose reduction. Median capecitabine dose was 1,250 mg/kg twice daily (inter-quartile range (IQR) 1,061-1250).

Potential reasons for discrepant results

There was variability within study design between the most relevant phase III studies discussed above, which are relevant (65, 77, 78). In addition, it is also appropriate to compare these new studies with the prior Japanese phase III study (14) to put study designs into context and highlight changes in practice over time (**Table 1**). Studies can be grouped according to the chemotherapy backbone employed: fluoropyrimidine-based (Takada and BILCAP) and gemcitabine-based (BCAT and PRODIGE-12/ACCORD-18). Only one of the studies tested doublet chemotherapy (PRODIGE-12/ACCORD-18). Overall, the largest study dedicated to CCA/GBC was the BILCAP study, which also recruited patients over a longer time period (total of 11 years).

There are two main differences identified regarding study design when comparing the modern studies (65, 77, 78), with the older Takada study (14). The first is that current study designs allowed time for adequate recovery from surgery before starting adjuvant chemotherapy (maximum 12-16 weeks), whereas Takada et al. administered adjuvant chemotherapy at the time of surgery and continued 1 week after. Such recovery time may confer significant benefit by improving tolerance of adjuvant therapy, as has been shown in another disease group (142). A second difference is the current preference for administering adjuvant therapy for a pre-defined period of time (typically 6 months (65, 77, 78)), rather than continuing chemotherapy until disease progression (14).

The study design included 1:1 randomisation for all studies, with stratification factors, which included main prognostic factors such as the primary site (all studies), resection margins (BCAT, PRODIGE-12/ACCORD-18) and lymph node metastases (BCAT and PRODIGE-12/ACCORD-18). Even though the BILCAP study did not stratify according to lymph node metastases, such characteristics were well balanced between study arms, and it is unlikely that this had any impact on findings. Similarly, BCAT and PRODIGE-12/ACCORD-18, did not stratify according to performance status but the rate of Eastern Cooperative Oncology Group (ECOG) performance status 2 patients (the group most likely to impact prognosis) was well balanced between study arms. It is worth highlighting that all the studies stratified according to the institution, an important factor to take into account at the time of evaluating treatment strategies that include any form of surgery. In fact, the BILCAP trial required patients to undergo surgery in “specialist hepato-pancreato-biliary centres” which is mandated practice in the United Kingdom; such information in other studies was not specified. This may be of relevance, especially because the number of study sites involved was similar for all the studies, with the corresponding heterogeneity in surgical expertise. Finally, if resection margins are to be used as a stratification factor, it is important to understand its definition, which varies between countries. The College of American Pathologists defines R1 as tumour cells present at the margin, while the Royal

College of Pathologists (United Kingdom) also includes tumour cells within 1 mm of the margin as R1 (143-145); the latter definition was used in the BILCAP trial only.

The primary end-point selected for each study, associated sample size calculations and planned statistical analyses require careful discussion. The majority of studies chose OS as a primary end-point, with the exception of PRODIGE-12/ACCORD-18, which selected RFS. Analysis of primary end-point in the ITT population was selected for both PRODIGE-12/ACCORD-18 and BILCAP. Even though the BCAT study analysed the primary and secondary end-points excluding the non-eligible randomised patients (likely to represent the per-protocol population), the study population only varied by 1 patient in the control arm, and therefore it is unlikely that this impacted on study findings. BILCAP was the only study that pre-specified that the primary end-point would be analysed adjusted for stratification factors, and which also pre-defined a sensitivity analysis adjusting the analysis for additional prognostic factors. For both, PRODIGE-12/ACCORD-18 and BILCAP, there was a plan for analysis of primary and secondary end-points in the per-protocol populations. Definition of such populations vary slightly between both studies, but there was a component of meeting eligibility criteria and receiving a minimum pre-set amount of adjuvant therapy in both. Interestingly, the percentage of patients excluded from the ITT population at the time of defining the per-protocol population was 3.8% in BILCAP but much higher in PRODIGE-12/ACCORD-18 (20.9%). If a proportion of these were due to early post-operative recurrence, it may highlight the need for better selection of patients for resection. Some recent work has been done in this area, and additional imaging prior to surgery in the form of ^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}FDG-PET) may have a role, especially for identification of occult metastatic disease (146).

Regarding the sample size and assumptions related to these sample size calculations, it is worth highlighting that some of the studies aimed for a very ambitious benefit, such as the PRODIGE-12/ACCORD-18 (study powered for HR of 0.6 for RFS) or the study by Takada study (aimed to identify an absolute difference in 5-year OS rate of 20%). This resulted in studies underpowered to identify small but perhaps still clinically meaningful differences, which would require larger, longer duration, and more costly studies to reliably confirm of refute.

In addition to the sample size, the maturity of the data is of relevance. Only two of these studies had actually reached the maturity of the data for analysis of the pre-defined primary end-point: PRODIGE-12/ACCORD-18 and BILCAP. Therefore, the other two studies are underpowered for any further conclusions, including the primary end-point for which the study was theoretically powered.

When analysing RFS and comparing between studies, one wonders why capecitabine showed a benefit in term of RFS while GemOx did not. As mentioned above, the PRODIGE-12/ACCORD-18 study was adequately-powered and data maturity in terms of RFS events was appropriate. In fact, median RFS in

the control arms are similar (18.5 (PRODIGE-12/ACCORD-18) vs 17.5 (BILCAP) months), suggesting that both study populations were comparable, at least with respect to RFS time. One of the potential explanations may be in the length of follow-up. When reporting HRs, the separation of the respective curves in the Kaplan-Meier graph is relevant. In the BILCAP trial, the separation of the curves for RFS initiated at the beginning of follow-up and runs in parallel throughout (HR 0.75 in the ITT population). In contrast, in the PRODIGE-12/ACCORD-18 study, the curves converge at month 48. This may reflect the fact that the median follow-up for PRODIGE-12/ACCORD-18 trials was shorter (median 46.5 months) than BILCAP (median follow-up 60 months). This could also explain why the median RFS for the GemOx arm in this study was longer than for capecitabine in the BILCAP study (30.4 (PRODIGE-12/ACCORD-18) vs 24.4 (BILCAP) months), which, despite overlapping 95% CIs, may represent overoptimistic estimations due to shorter follow-up for censored patients in PRODIGE-12/ACCORD-18. The fact that median RFS in PRODIGE-12/ACCORD-18 was "*achieved at a plateau with the largest separation between the curves*" could also make the median RFS less representative of the true difference (78). The fact that radiological assessment was more frequently performed for the PRODIGE-12/ACCORD-18 trial (3-monthly during the first 2 years, 6-monthly thereafter) than for the BILCAP trial (6-monthly during the first 2 years, annually thereafter) is unlikely to have impacted on the above-mentioned differences, since it would have skewed the findings in the contrary direction.

In terms of OS, both the control and the experimental median OS were longer in the PRODIGE-12/ACCORD-18 study when compared to BILCAP. Once again, it is unlikely that this represents a real effect or any differences between study populations, and is more likely to be a reflection of overoptimistic estimations due to limitations derived from shorter follow-up and lack of OS data maturity. In addition to differences in follow-up time, power and data maturity, there are some imbalances in the subpopulations of BTCs recruited between studies. The BCAT study limited recruitment to eCCA alone, with almost half split between hCCA and dCCA; this was also the most prevalent population in BILCAP. The PRODIGE-12/ACCORD-18 had a predominance of iCCA. Whether this impacts on findings cannot be fully excluded, since there is some evidence suggesting that iCCA may have a more favourable natural history (147), likely reflective of different molecular biology (91). It has also been suggested that in view of worse response to GemOx in previous studies for the GBC population (148), the fact that resected GBC were included in PRODIGE-12/ACCORD-18 could have negatively affected the findings (78).In addition to the differences in the subtypes of BTC recruited into the different studies, there was also a higher proportion of patients harbouring poor prognosis factors (such as R1 and N1 disease, previously reported to be the subgroups benefiting the most from chemotherapy (105, 141)) in the BILCAP study and could maybe also explain the positive findings of this study (78).

One of the main criticisms of the BILCAP study is the limited absolute reduction in relapse rate (65% vs 60%) when the study did not show a benefit in RFS after the 24 months from randomisation (HR 1.48 (95% CI 0.80-2.77); p-value 0.21), raising the possibility "that capecitabine only defers recurrence" (149). Relapse rate reported in all studies was similar, highlighting that this is an ongoing issue to resolve. The 5-year survival data from the BILCAP trial is awaited; if 5-year OS benefit is confirmed, a potential real effect of capecitabine increasing the rate of cure and not only delaying recurrence may then be confirmed

The fact that recurrent disease is mainly in the form of distant metastases was already known and is the rationale for adjuvant strategies with systemic chemotherapy. However, at the time of recurrence, clinicians and patients are facing among others, two main issues. Firstly, the majority of patients will have recurrent disease which is not amenable to surgical options, therefore entering a palliative pathway with the implications on prognosis that this implies. Secondly, the selection of the first-line palliative chemotherapy is often influenced by which adjuvant therapy the patient previously received, and the time between the adjuvant therapy and recurrence. Data on palliative treatment were not recorded in the BILCAP study but were reported in the PRODIGE-12/ACCORD-18 study and highlight an important message. Choice of first-line chemotherapy was most frequently gemcitabine-based regimens in the observation arm and fluoropyrimidine-based regimens in the GemOx arm; interestingly, post-relapse OS tended to be worse in the GemOx arm (median OS 8.0 months) vs observation arm (median OS 15.2 months); HR 1.55 (95% CI 0.98-2.47); p-value 0.06. Current evidence supports use of cisplatin and gemcitabine as the standard of care in the first-line setting for advanced disease. However, the evidence for fluoropyrimidine-based chemotherapy is reserved for the second line setting. Patients who received adjuvant GemOx potentially did not receive the most effective first-choice palliative treatment. Additional questions include: are adjuvant strategies that potentially compromise first-line advanced disease chemotherapy adequate? Are we selecting clones of cells resistant to gemcitabine and oxaliplatin when these patients recur? These will require further research and need to be taken into account in further study design.

Summary of current guidelines and recommendations

ESMO guidelines (last updated in 2016) have not yet been updated and adjusted to include the latest evidence (65, 77, 78). Therefore, statements regarding adjuvant recommendations do not provide strong recommendations in favour of a specific strategy and do, in fact, highlight the lack of quality evidence at the time of these being issued. Authors concluded that "adjuvant therapy (radiotherapy, chemo-radiotherapy or chemotherapy alone) may be offered to patients on the understanding that the evidence base is weak, and only after risk–benefit assessment; participation in clinical trials should be encouraged" (7).

National Comprehensive Cancer Network (NCCN) guidelines were updated January 2019 (150), prior to the publication of the BILCAP study (77). Current NCCN guidelines support the use of adjuvant chemotherapy and chemo-radiotherapy for CCA and GBC, regardless of R0/1 and N0/1 status for GBC and eCCA. The only exception is for patients with completely resected (R0) iCCA, for whom chemo-radiotherapy is not recommended. However, the NCCN guidelines do not specify a recommended chemotherapy schedule and do suggest that schedules active in the metastatic setting could be employed: *"There are phase II trials that support the following combinations: gemcitabine/cisplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. The phase III BILCAP study shows improved overall survival for adjuvant capecitabine in the per-protocol analysis, but the study is not yet published, and the overall survival did not reach statistical significance in the intent-to-treat analysis"*.

Following the latest evidence published, an urgent need for updated guidelines was recognised. Based on this, the ASCO guidelines were updated (95) and, based on the BILCAP trial results, recommended adjuvant capecitabine for a period of six months following curative resection of BTCs (CCA and GBC) as a new standard of care (95). Authors stated that the role of chemo-radiotherapy remained unclear and suggested its use for patients with eCCA with R1 resection (95, 151) or other high-risk factors.

Current caveats and future perspectives

We have learned multiple lessons from past clinical trials. Researchers agree on the fact that a recovery time period is required post-surgery prior to starting adjuvant therapy; based on findings from the BILCAP trial, it does seem that a maximum period of 12-16 weeks is sufficient, without adversely impacting on patient outcomes. In addition, administration of chemotherapy during a limited period of time (rather than until disease recurrence) is accepted as standard practice in the adjuvant setting and has been shown to be safe, with very limited long-term toxicity. Finally, based on the data available, chemotherapy based on fluoropyrimidines seems to be preferable, since this was used in the only two positive studies to date (14, 77). However, emerging data on molecular targets in BTC may result in novel future adjuvant designs incorporating these findings.

There are multiple clinical trials ongoing to further explore the role of adjuvant chemotherapy for BTC (**Table 2**). However, multiple questions remain unanswered (**Figure 3**).

There is a need to standardise the definition of some of the risk factors (such as R1), and also an urgent need to include these as stratification factors and to pre-plan adjusted statistical analysis. Typical risk factors such as primary tumour site, resection margins and lymph node metastases are the most important ones, but have not, yet, resulted in design alteration. Should these be used as stratification

to enrich for patients at risk of relapse in future studies? Is adjuvant therapy a “one size fits all”, as it seems at the moment? The institution should also be included as a stratification factor in studies exploring an experience-dependent intervention, such as surgery.

Similar to the need for identification and use of risk factors for tailored treatment strategies, we are in urgent need of biomarkers to better select which patients are more likely to benefit from specific adjuvant strategies. In addition, there is a need for in-depth translational research to understand mechanisms of resistance and disease recurrence. In order for researchers to learn from every patient and every trial (even if negative), it is crucial to include tissue banking and translational research questions in future studies.

In addition, adequate patient selection is key, not only for adjuvant therapy but also for surgery. There is evidence supporting the use of ^{18}FDG-PET for identification of occult metastases in BTC and this is of huge relevance in this setting (146); to reduce the number of patients undergoing unnecessary surgery and to avoid delays in initiating systemic therapy in patients with “occult” metastatic disease.

Adequate study design is crucial. The time for small phase II studies has passed and the community is now in need of further phase III randomised studies, comparing experimental arms with an active (non-observational) control arm (currently: capecitabine). Clinically-meaningful but achievable assumptions are required at time of sample size calculations; to design adequately-powered studies able to provide mature and quality data to answer the question that is being asked. Sample size calculations may require revision during the study period to ensure that assumptions made at the time of study design are still accurate and relevant. Over the years, there has been some discrepancy regarding the most adequate primary end-point for adjuvant studies (RFS vs OS). The caveats of these two are to be taken into account, since we probably need power to show benefit in both of them; unfortunately, RFS may not a good surrogate for OS due to the impact of subsequent lines of therapy on OS. Related to the study design, we have reached a point in which the feasibility of performing dedicated adjuvant trials in BTCs has been shown, despite their infrequency. However, long study durations cannot be ignored. Length of studies does not only depend on required follow-up per patient (directly related to primary end-point selected), but also the fact that all studies until now have been performed in single countries. The rationale for this approach has been related to funding and the fact that they were all investigator-led studies. Securing funding for performing multi-national studies is challenging, if not impossible. As a clinical community, we need to re-think how we collaborate in future studies. Biliary tract researchers have been successful at recruiting to randomised phase III trials in the advanced setting, when performed with adequate funding, to allow sites to open in multiple countries, even when small subpopulations of a rare cancer have been targeted (92). It is likely that researchers have to be imaginative and find ways around these issues, since it is unlikely

that third-parties (e.g. industry) will be interested in adjuvant trials exploring well-known chemotherapy agents and radiotherapy.

Relapse rate remains high, with 60% reported with capecitabine in the BILCAP study (77). New chemotherapy agents and novel combinations are probably required to overcome this issue, together with the additional challenge of how to implement some of the emerging targeted therapies in the adjuvant scenario. In addition, the role of radiotherapy is still to be elucidated, and randomised phase III studies adequately powered to answer these questions are urgently required. It is likely that patients with a higher risk of local recurrence (R1 disease) are likely to benefit more from these approaches. Emerging strategies such as peri-operative treatment and neo-adjuvant strategies are also to be explored. As previously mentioned, the schedule chosen in the adjuvant setting may impact on the first-line palliative chemotherapy that patients are exposed to, and on occasions there has been an apparent detrimental effect (78). It will be interesting to see whether a similar effect will be demonstrated in the ongoing ACTICCA-1 clinical trial (cisplatin and gemcitabine versus capecitabine; NCT02170090) and if so, this will need to be addressed in future study design, to ensure that first-line palliative treatment choice is not compromised.

Conclusion

Despite the reservations regarding the findings of the BILCAP trial, this study has changed the paradigm of adjuvant therapy, establishing capecitabine as the new standard of care for resected CCA and GBC. Unfortunately, the relapse rate remains high and it is clear that not all patients benefit from such adjuvant therapy, necessitating further randomised studies exploring the role of novel strategies. Adequately-designed and properly powered studies with sufficient follow-up are required for development of adjuvant tools which will increase the cure rate for patients with CCA and GBC.

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Conflict of interest

Angela Lamarca: Travel and educational support from Ipsen, Pfizer, Bayer, AAA, SirtEx, Novartis, Mylan and Delcath. Speaker honoraria from Merck, Pfizer, Ipsen and Incyte. Advisory honoraria from EISAI, Nutricia Ipsen, and QED. Member of the Knowledge Network and NETConnect Initiatives funded by Ipsen.

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Richard Hubner: no conflict of interest to declare

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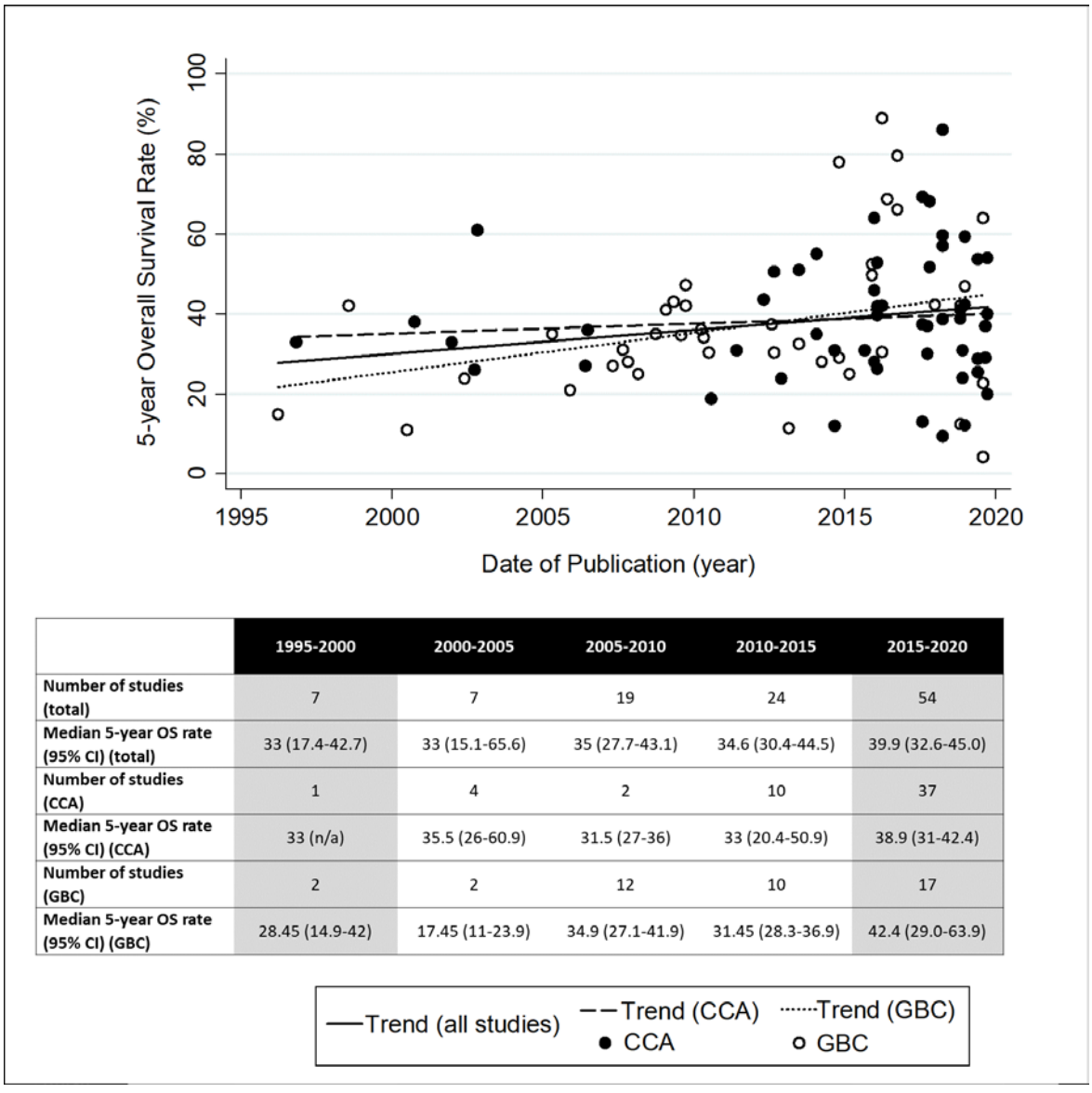
Tables and figures

Figure 1: Reported 5-year overall survival rate for patients with resected CCA and GBC during the last 15 years are shown in the figure below

Adapted and updated from (13). Data extracted from studies reporting 5-year survival rate for patients with resected disease (last updated October 2019) (5, 14-76). Studies which included data jointly for CCA and GBC were not included (77, 78). CCA: cholangiocarcinoma; GBC: gallbladder cancer; CI: confidence interval.



	1995-2000	2000-2005	2005-2010	2010-2015	2015-2020
Number of studies (total)	7	7	19	24	54
Median 5-year OS rate (95% CI) (total)	33 (17.4-42.7)	33 (15.1-65.6)	35 (27.7-43.1)	34.6 (30.4-44.5)	39.9 (32.6-45.0)
Number of studies (CCA)	1	4	2	10	37
Median 5-year OS rate (95% CI) (CCA)	33 (n/a)	35.5 (26-60.9)	31.5 (27-36)	33 (20.4-50.9)	38.9 (31-42.4)
Number of studies (GBC)	2	2	12	10	17
Median 5-year OS rate (95% CI) (GBC)	28.45 (14.9-42)	17.45 (11-23.9)	34.9 (27.1-41.9)	31.45 (28.3-36.9)	42.4 (29.0-63.9)

Table 1: Main characteristics of available phase III studies exploring the role of adjuvant treatment for GBC and CCA.

iv: intravenously; CCA: cholangiocarcinoma, GBC, gallbladder cancer; dCCA: distal cholangiocarcinoma; hCCA: hilar cholangiocarcinoma; eCCA: extrahepatic cholangiocarcinoma; iCCA: intrahepatic cholangiocarinoma; OS: overall survival; RFS: relapse-free survival; TTD: time to definitive deterioration; HRQOL: health-related quality of life; ITT: intention-to-treat; IDMC: independent data monitoring committee; Mod dif: moderately differentiated; Poorly dif: poorly differentiated; Gem: gemcitabine, GemOx: gemcitabine and oxaliplatin; Cap: capecitabine; IQR: interquartile range; obs: observation; n: number of patients; %: percentage; R1: positive resection margins; R0: clear resection margins: N0: negative lymph nodes; N1: presence of metastatic regional lymph nodes.

	Takada et al (14)	**BCAT (65)**	**PRODIGE-12/ACCORD-18 (78)**	**BILCAP (77)**
Study design	Randomised phase III; open label	Randomised phase III; open label	Randomised phase III; open label	Randomised phase III; open label
Study arms	Mitomycin C (MMC; 6 mg/m^2 at the time of surgery) and 5-fluorouracil (**5-FU**; 310mg/m^2 (iv) during 5 consecutive days on week 1 and 3 after surgery followed by daily **oral** 100mg/m2 from week 5 until disease recurrence) (MF arm) versus surgery alone (control arm)	Gemcitabine (**Gem** arm; 1000mg/m^2, administered iv on days 1, 8 and 15 every 4weeks for 6 cycles) vs surgery alone (control arm); time of chemo initiation not specified	Gemcitabine and oxaliplatin (**GemOx** arm; iv Gem 1,000mg/m2 on day 1 and Ox 85mg/m^2 on day 2 every 2 weeks for 12 cycles) vs surgery alone (control arm); randomisation had to take place within 3 months of surgery and GemOx started within 1 week from randomisation.	Capecitabine (**Cap** arm; 1250mg/m² **orally** twice daily on days 1–14 of a 21-day cycle, for 8 cycles) vs surgery alone (control arm) Cap started up to 12 weeks from surgery, with a maximum extension to 16 weeks from surgery.
Recruitment period	April 1986-June 1992	September 2007-31 January 2011	July 2009-February 2014	March 2006-December 2017
Number of sites	31	48	33	44
country	Japan	Japan	France	United Kingdom
Randomisation; Stratification factors	1:1; stratified according to institution and primary site (CCA, GBC, pancreas, ampullary).	1:1; stratified according to lymph node status, resection margin status, primary site (hCCA vs dCCA) and institution.	1:1 random; stratified according to primary site (iCCA vs eCCA vs GBC), resection margin, lymph node involvement, and institution.	1:1; stratified according to institution, primary site (iCCA vs hCCA vs dCCA vs GBC), resection margin, and performance status.
Sample size (randomised pts; ITT population)	508 patients randomised: CCA (n=139), GBC (n=140)	226 patients randomised (Gem (n=117) vs control (n=109))	196 patients: 97 (GemOx; 95 included; 2 withdrew consent) vs 99 (control)	447 patients; 223 (Cap) vs 224 (control)
Sample size (per-protocol population)	CCA: n=118: MF group (n=58) vs control (n=60) group) GBC: n=112: MF group (n=69) vs control (n=43) group)	225 patients (Gem (n=117) vs control (n=108)) 1patient excluded: 0.4% of total population	155 patients: 73 (GemOx) vs 82 (control) 41patient excluded: 20.9% of total population	430 patients; 210 (Cap) vs 220 (control) 17 patient excluded: 3.8% of total population
Primary end-point	OS (time from the day of surgery to death from any cause)	OS (time from randomization to death from any cause)	RFS (time from randomization to relapse or death from any cause)	OS (time from to death from any cause or cancer-related death)

			Co-primary end-point: time to definitive deterioration (TDD) of HRQOL	
Pre-planned analysis (primary end-point)	Per protocol population; primary end-point analysed separately for each disease group separately	Per-protocol population; including all eligible randomised patients Pre-specified subgroup analysis according to margin status, lymph node status and primary tumour site	ITT population; including all randomised patients Pre-specified exploratory per-protocol analysis was planned including patients who met inclusion criteria and who had received at least 50% of the chemotherapy dose during the first six cycles)	ITT population; including all randomised patients; adjusted to stratification factors excluding surgical centre Pre-specified sensitivity analysis in the ITT population, adjusting the treatment effect for identified prognostic factors
Secondary end-points	RFS	RFS, subgroup analysis and toxicity	OS, toxicity, and exploratory translational end points	Per-protocol analysis (excluding ineligible patients and those failing to complete at least one cycle of Cap) of OS/RFS, RFS (ITT population), toxicity, health economics, and quality of life
Frequency of imaging assessment	Not specified	Every 3 months during the first 3 years after enrolment, and every 6 months thereafter until the end of follow-up (at least 5 years from registration).	Every 3 months from randomization for 2 years, and then every 6 months for the next 3 years.	Every 6 months for the first 24 months and at annual intervals with clinical review for up to 5 years.
Assumptions for sample size calculation	A minimum of 60 patients per group required; Assumed 5-year OS rate 15% in the control group; postulated 5-year OS increase by 20% (35%) MF arm; 5% alpha (two-sided), power 80%. Number of events at time of analysis:	A total of 300 patients (189 events) required; Postulated HR OS 0.85; 5% alpha (two-sided), power 80%. Interim analysis: performed when enrolled 200 patients; alpha error adjusted (<5%) to control for multiplicity for the primary endpoint; patient recruitment early terminated due to lack of recruitment. Number of events at time of analysis: total 119: 62 (Gem) and 57 (observation)	RFS was considered as the primary endpoint for statistical power calculation; A total of 190 patients (126 events) required; Postulated HR OS 0.6; 5% alpha (two-sided), power 80%. Power to show a difference in global HRQOL of at least 5 points with 180 patients included was 80%. Number of events at time of analysis: total 126: 59 (GemOx) and 67 (observation)	A minimum of 360 patients (270 events) required; Assumed 24-month OS rate 20% in the control group; postulated 24-month OS increase by 12% (32%) Cap arm; equivalent to HR 0.71; 5% alpha (two-sided), power 80%. IDMC recommended that the final analyses be done once 234 events had accrued. Revisited OS rate (60%) in the control group; increase by 11% (71%); equivalent to HR 0.69; 5% alpha (two-sided), power 80%. Number of events at time of analysis: total 243: 114 (Cap) and 131 (observation)
BTC subtype	CCA (n = 118; 58 in the MF group and 60 in the control group) and GBC (n = 112; 69 in the MF group and 43 in the control group)	All eCCA: 102 hCCA and 123 dCCA	Any CCA/GBC: predominance of iCCA (44%)	CCA/GBC: most patients had dCCA followed by hCCA; only 19% in the Cap arm and 18% in the observation arm were iCCA.
Stage and distribution of prognostic factors	GBC: stage III (33% MF vs 33% observation) stage IV (46% MF vs 60% observation) Curative surgery (45% MF vs 47% observation) CCA: stage III (48% MF vs 37% observation) stage III (26% MF vs 43% observation)	N1 (35.9% Gem vs 33.3% observation) stage II (51.3% Gem vs 55.6% observation) stage III (14.5% Gem vs 13.0% observation) R1 (9.4% Gem vs 13.0% observation) Mod dif (45.3% Gem vs 59.3% observation)	Predominance of iCCA (44%); N1 (36%) and R1 (13%); these characteristics were balanced between the study arms iCCA (43% GemOx vs 46% observation) hCCA (11% GemOx vs 5% observation) dCCA (28% GemOx vs 28% observation) GBC (18% GemOx vs 21% observation) N1 (35% GemOx vs 36% observation)	iCCA (19% Cap vs 19% observation) hCCA (29% Cap vs 28% observation) dCCA (34% Cap vs 36% observation) GBC (17% Cap vs 18% observation) N1 (48% Cap vs 46% observation) R1 (38% Cap vs 38% observation) Stage II (61% Cap vs 64% observation) Stage III (13% Cap vs 8% observation)

	Curative surgery (59% MF vs 63% observation) R0/1 not reported	Poorly dif (12.8% Gem vs 12.0% observation)	R1 (14% GemOx vs 12% observation)	
Completion of chemotherapy and toxicity profile	Good compliance (80%) was achieved with MF	61 patients (52.1%) completed chemotherapy (with (32.8%) or without (67.2%) dose reduction); 18 patients stopped Gem due to need for dose reduction to below 60% and 6 due to delay >28 days	Gem median 10 cycles (mean 9.7); Ox median 10 cycles (mean 8.5) At 12 months, prevalence of sensory neuropathy was: grade 1 (10%), grade 2 (6%), and grade 3 (4%) in the GEMOX arm.	44% of patients had at least one grade 3 toxicity; <1% had grade 4 cardiac ischaemia or infarction Serious adverse events (21%) 55% of patients completed chemotherapy course; 10 patients (4%) had 0 cycles; median Cap dose was 1250mg/m2 twice daily (IQR 1061 - 1250mg/m2) 46% had at least one dose reduction; 32% discontinued treatment because of toxicity (hand-foot syndrome (14%), diarrhoea (13%)
Median follow-up and maturity of data	All patients were followed-up for 5 years; median follow-up not provided	Median follow-up was 79.4months OS: During follow-up 62/117=52.9% (Gem) and 57/108=52.8% (observation) died. Relapse: data maturity not reported.	Median follow-up of 46.5 months OS: During follow-up 41/95=43.2% (GemOx) and 41/99=41.4% (observation) died. Relapse: During follow-up 59/95=62.1% (GemOx) and 67/99=67.7% (observation) progressed.	Median follow-up of 60 months OS: During follow-up 114/223=51% (Cap) and 131/224=58% (observation) died. Relapse: During follow-up 134/223=60% (Cap) and 146/224=65% (observation) progressed.
Results primary end point	OS (GBC): 5-year survival rate in gallbladder carcinoma patients was significantly better in the MF group (26.0%) compared with the control group (14.4%); p-value 0.0367 OS (CCA): not reported; p-value >0.05	OS: No significant differences in OS (median 62.3 months (Gem) *vs* 63.8 (observation); HR 1.01 (95% CI 0.70-1.45; p-value 0.964	RFS: No differences in RFS (median 30.4 months (95% CI 15.4-43.0) (GemOx) vs 18.5 (95% CI 12.6-38.2) (observation); HR 0.88 (95% CI 0.62-1.25); p-value 0.48 The per-protocol analysis confirmed the findings (HR, 0.86 (95% CI 0.59-1.27); p-value 0.45. No difference in TTD of global HRQOL	OS: Primary analysis, ITT OS (adjusted for minimisation factors other than surgical centre): median was 51.1 months (95% CI 34.6-59.1) (Cap) vs 36.4 (95% CI 29.7-44.5) (observation); HR 0.81 (95% CI 0.63-1.04); p-value 0.097 ITT OS, sensitivity analysis (adjusted for stratification factors and other prognostic factors such as nodal status, grade of disease and sex): HR 0.71 (95% CI 0.55-0.92); p-value 0.010 Per protocol OS, sensitivity analysis (adjusted for minimisation factors other than surgical centre): median was 53.0 months (95% CI 40-not reached) (Cap) vs 36.0 (95% CI 33-44) (observation); HR 0.75 (95% CI 0.58-0.97); p-value 0.028
Subgroup analysis (primary end-point)	Not reported	Trend towards a benefit for women, and lack of benefit among patients with ECOG performance status 1.	Group with less benefit was GBC No specific group benefited from adjuvant GEMOX	More marked benefit of Cap in men (HR 0.70 (95% CI 0.50-0.99) and poorly differentiated disease (HR 0.60 (95% CI 0.39-0.93).
Secondary end-points	RFS (GBC): 5-year RFS rate 20.3% (MF group) vs 11.6% (observation); median 11.9 months (MF group) vs 12.3 (observation); p-value 0.0210 RFS (CCA): 5-year RFS rate 26.7% (MF group) vs 24.1% (observation); p-value >0.05	RFS: median 36.0 months (Gem arm) vs 39.9 (observation); HR 0.93 (95% CI 0.66-1.32); p-value 0.693	OS: median of 75.8 months (95% CI 34.4-not reached) (GemOx) vs 50.8 (95% CI 38.0-not reached); HR 1.08 (95% CI 0.70-1.66); p-value 0.74	RFS (first 24 month period), ITT (adjusted for minimisation factors other than surgical centre): median 24.4 months (95% CI 18.6-35.9) (Cap) vs 17.5 (95% CI 12.0-23.8); HR 0.75 (95% CI 0.58-0.98); p-value 0.033 RFS (first 24 month period), per-protocol (adjusted for minimisation factors other than surgical centre): median 25.9 months (95% CI 19.8-46.3) (Cap) vs 17.4 (95% CI 12.0-23.7); HR 0.70 (95% CI 0.54-0.92); p-value 0.0093

				RFS (period from 24-60 months), ITT (adjusted for minimisation factors other than surgical centre): HR 1.48 (95% CI 0.80-2.77); p-value 0.21
Relapse rate	79.7% (MF arm; GBC) 88.4% (observation; GBC)	53.8% (Gem) 56.5% (Obs)	62.1% (GemOx) 67.7% (observation)	60% (Cap) 65% (Obs)
Relapse pattern	Not reported	Location of first relapse similar between both groups: liver (most frequent), local site, peritoneum, and lymph nodes	Similar proportion of metastatic recurrence in both arms: 75% (GemOx) and 71% (observation)	Not reported
Subsequent therapy	Not reported	Of the 124 patients with relapse: 92 chemotherapy, 9 radiotherapy, 8 surgical resection.	Most frequently gemcitabine-based regimens in the surveillance arm and fluoropyrimidine-based regimens in the GemOx arm Post-relapse OS tended to be worse in the GemOx arm (median OS 8.0 months) vs observation arm (median OS 15.2 months); HR 1.55 (95% CI 0.98-2.47); p-value 0.06	Follow-up treatment for patients who had disease recurrence was not recorded.

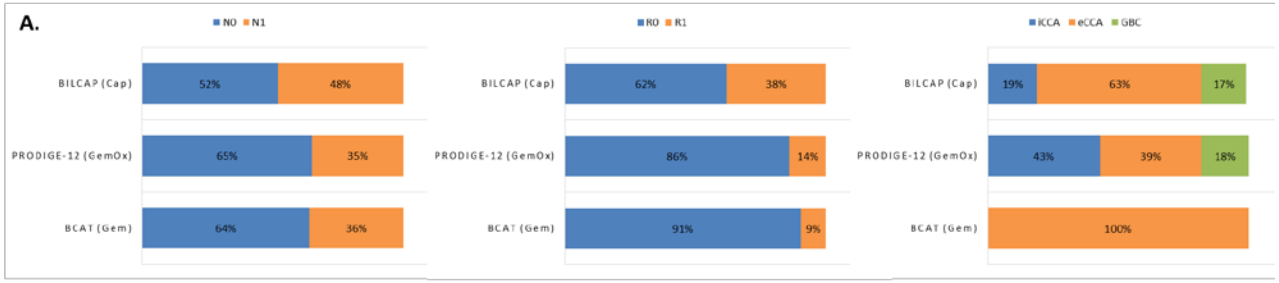
Table 2: Ongoing trials studying the efficacy of adjuvant treatment in cholangiocarcinoma and gallbladder cancer (www.clinicaltrials.gov; last accessed October 2019).

Study/Country (registration number)	Patient number	Population	Arms	Primary endpoint	Expected completion
Germany - ACTICCA-1 NCT02170090	781	Cholangiocarcinoma and gallbladder	Capecitabine vs Cisplatin-Gemcitabine Phase III	Relapse-free survival	April 2023
South Korea NCT03079427	100	Extrahepatic cholangiocarcinoma	Capecitabine vs. Cisplatin-Gemcitabine Phase II	2-year disease-free survival	April 2022
China NCT02548195	286	Intrahepatic cholangiocarcinoma	Capecitabine vs. Gemcitabine-Oxaliplatin Phase III	Relapse-free survival	December 2018
China NCT04077983	40	Intrahepatic cholangiocarcinoma	Gemcitabine-Nab-paclitaxel Phase II	Relapse-free survival	September 2022
China - AdBTC-1 NCT03779035	460	Cholangiocarcinoma and gallbladder	Gemcitabine vs Capecitabine Phase III	Relapse-free survival	December 2023
China NCT03702491	138	Gallbaldder cancer	Apatinib with SOX (Tegafur, Oxaliplatin) vs SOX alone	Progression-free survival	August 2020

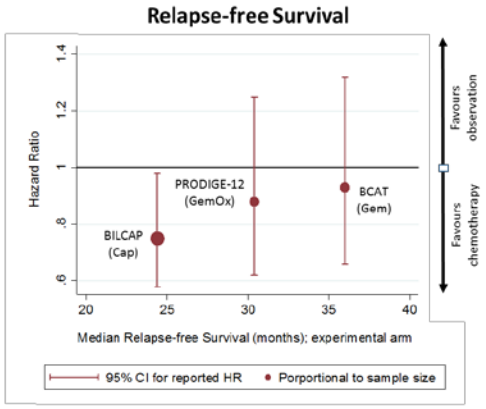
Figure 2: Summary of main findings and differences within the ecent phase III trial exploring the role of adjuvant chemotherapy in biliary tract cancer.

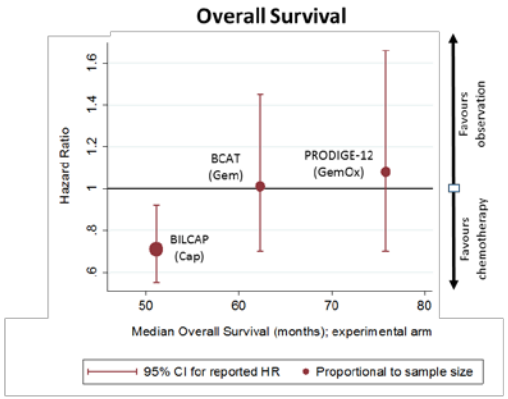
Three phase III trials have been recently published exploring the role of adjuvant chemotherapy in resected cholangiocarcinoma and gallbladder cancer. The trials differ in some of the baseline characteristics which may explain why only the BILCAP trial (capecitabine vs observation) was the only study showing benefit in favour of adjuvant chemotherapy in resected biliary tract cancer. **Figure 2.A** shows main differences in study characteristics. **Figure 2.B** provides a graphic representation of HR for Relapse-free and Overall survival, with further details summarised in **Figure 2.C**.

iCCA: intrahepatic cholangiocarcinoma; eCCA: extrahepatic cholangiocarcinoma; GBC: gallbladder cancer; N0: no evidence of lymph node metastases; N1: presence of lymph node metastases; R0: clear resection margins; R1: affected resection margins (including tumour within 1 mm for the BILCAP trial); Cap: capecitabine, Gem: gemcitabine; GemOc: gemcitabine and oxaliplatin; HR: Hazard Ratio; CI: confidence interval. *Hazard Ratio in the ITT (intention-to-treat) population (sensitivity analysis) is presented for the BILCAP trial (Overall Survival).



B.





C.

	Relapse-free Survival (months)
Bilcap (Cap vs Observation)	Median 24.4 (95% CI 18.6-35.9) vs 17.5 (95% CI 12.0-23.8) HR 0.75 (95% CI 0.58-0.98)
PRODIGE-12 (GemOx vs Observation)	Median 30.4 (95% CI 15.4-43.0) vs 18.5 (95% CI 12.6-38.2) HR 0.88 (95% CI 0.62-1.25)
BCAT (Gem vs Observation)	Median 36.0 vs 39.9 HR 0.93 (95% CI 0.66-1.32)

	Overall Survival (months)
Bilcap (Cap vs Observation)	Median 51.1 (95% CI 34.6-59.1) vs 36.4 (95% CI 29.7-44.5) HR* 0.71 (95% CI 0.55-0.92)
PRODIGE-12 (GemOx vs Observation)	Median 75.8 (95% CI 34.4-nr) vs 50.8 (95% CI 38.0-nr) HR 1.08 (95% CI 0.70-1.66)
BCAT (Gem vs Observation)	Median 62.3 *vs* 63.8 HR 1.01 (95% CI 0.70-1.45

Figure 3: Future perspectives and unanswered questions

N1: lymph node positivity; R1: positive resection margins; CCA: cholangiocarcinoma; GBC: gallbladder cancer; ^{18}FDG-PET: ^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography; RT: radiotherapy;