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Adjuvant chemotherapy in resected bile duct cancer: A systematic review and meta-analysis of randomized trials

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ABSTRACT

Background: The role of adjuvant chemotherapy (ACT) for resected biliary tract cancer (BTC) is still unclear and there is no specific recommendation by international guidelines.
Aim: To perform a meta-analysis of randomized clinical trials (RCTs) to better define the clinical benefit and risks of ACT or observation in resected BTC.
Method: A systematic literature search of Pubmed, Embase, and the Cochrane Library was performed up to April 2019. A meta-analysis was carried out using the random effects model.
Results: ACT provided a mild improvement in recurrence free survival (RFS) (HR:0.83, 95%CI 0.69-0.99) and no effect on overall survival (OS) (HR:0.91, 95%CI 0.75–1.09). Similarly, ACT showed no effect on OS in lymph-node positive subgroup (HR:0.84, 95% CI 0.65–1.08) and surgical margin positive subgroup (HR:0.95, 95%CI 0.69–1.31). Moreover, ACT led to a substantial increase of chemotherapy-associated adverse events (RR:3.03, 95%CI 2.22–4.15).
Conclusion: ACT for resected BTC patients modestly improved RFS with no effect on OS and a substantial increase in chemotherapy associated AEs.

1. Introduction

Biliary tract cancers (BTC) represent a rare (3% of all gastrointestinal cancers) and heterogeneous group of malignancies arising from the biliary ducts, including gallbladder cancers, intrahepatic and extrahepatic cholangiocarcinoma. In the USA, the annual incidence of BTC accounts for 1–2 cases per 100,000 population (Siegel et al., 2019). Although the improvements in multidisciplinary management, the prognosis of BTC remains poor, reporting approximately a median overall survival (OS) of 18–30 months after surgical resection with curative intent, mainly in patients with poor prognostic pathological features, such as involvement of regional lymph nodes (N+) or surgical margins (R+) (DeOliveira et al., 2007). Therefore, adjuvant chemotherapy (ACT) may play a key-role delaying disease recurrence and prolonging life expectancy of BTC patients. However, although a previous meta-analysis of mostly retrospective studies suggested a potential clinical benefit (Horgan et al., 2012), the role of ACT is still controversial. Moreover, most of the international guidelines do not define an optimal ACT regimen due to the low level of evidence. Given the availability of limited prospective data, the present study attempts to provide a comprehensive review of literature and a meta-analysis of randomized trials concerning the efficacy and safety of ACT for resected BTC.

2. Methods

The study design was a quantitative synthesis of randomized trials aiming to assess the efficacy and safety of ACT for resected BTC.

2.1. Study objective

The co-primary objectives of this study were to compare OS and recurrence free survival (RFS) between ACT and observation in patients with BTC who underwent surgery with curative intent. A pre-specified

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subgroup analysis was performed to assess OS in patients with N + or R1 + resected BTC. Secondary objective was to compare the incidence of treatment related adverse events (AEs), evaluated as ≥ grade 3–4 (G3-G4) toxicities.

2.2. Data sources and strategies

A literature search using PubMed, EMBASE, SCOPUS, Web of Science and The Cochrane Library was carried out with no date restriction up to April 2019. The search strategies included the keywords "biliary tract cancer", "gallbladder cancer", "cholangiocarcinoma", "adjuvant chemotherapy". A computerized search of the abstracts reported at ESMO and ASCO library was performed from 2000 up to April 2019 in order to identify relevant unpublished data. Specific keywords for each database and free text terms were combined with Boolean operators. Two reviewers (CM and MS) screened all full-text articles and abstracts independently. A third author (MM) reviewed the search results to apply the eligibility criteria to both sets of search outcomes and acted as an arbiter in case of disagreement between the two reviewers (CM and MS). Finally, a crosscheck of references from review articles and relevant studies on the same topic was performed to confirm retrieval of all possible pertinent trials. The work has been conducted accordingly PRISMA guidelines for reporting of systematic reviews (Moher et al., 2010).

2.3. Selection of the articles

Eligible studies had to fulfil the following criteria: (I) prospective randomized phase II and III trials designed to evaluate efficacy and safety of ACT versus observation in resected BTC; (II) the hazard ratio (HR) or risk ratio (RR) for OS and RFS of the intention-to-treat population and in the subgroup of N + and R + resected BTC, ≥ G3-G4 adverse events (AEs), had to be reported or could be computed from data presented in the selected studies.

Studies excluded from the analysis were those with the following characteristics: (i) non-randomized prospective studies designed to evaluate the efficacy and safety of ACT versus observation alone; (ii) retrospective studies; (iii) subgroup analysis of randomized prospective clinical trials, that allowed the enrolment of patients with both pancreatic cancers and resected BTC; (IV) on-going studies which had not yet been presented or published at the time of the literature search. No language restriction was applied. For each eligible study, we collected study design, main eligibility criteria, number of patients enrolled overall and into each treatment arm, number of OS, RFS and RR events, main ≥ G3-G4 AEs. Risk of bias in randomized controlled trials was assessed using the Cochrane Risk of Bias Tool (Higgins et al., 2011). Additional quality domains, including imprecision, inconsistency, indirectness, and potential for publication bias, were also assessed (Higgins and Green, 2011).

2.4. Statistical analysis

For data analysis, descriptive statistics were used to summarize baseline characteristics data. A quantitative synthesis (pooled-analysis) was performed on eligible randomized clinical trials if methodologically appropriate. For time-to-event data, HR and 95% of confidence intervals (CIs) were used to compare results. A HR < 1 indicates that the use of ACT yielded a lower probability of death or recurrence. A HR > 1 indicates that the use of ACT increases the probability of death or recurrence. Risk Ratio (RR) based on events data were calculated to compare ≥ G3-G4 AEs between ACT versus observation alone. A RR < 1 indicates that the use of ACT yielded a lower probability to develop lower ≥ G3–4 AEs compared to observation alone. A RR > 1 indicates that the use of ACT increases the probability of developing ≥ G3–4 AEs.

The Mantel-Haenszel method was used to obtain random-effects model estimates of the pooled HR (Mantel and Haenszel, 1959), since it is generally considered more appropriate than the fixed-models in the presence of significant heterogeneity among studies (Higgins and Thompson, 2002a). Standard checks of the homogeneity assumption were carried out (Higgins et al., 2002). The Higgins' I^2 index was computed to obtain a quantitative measure of the degree of inconsistency in the results of the studies included (Higgins and Thompson, 2002b). All statistical analysis and the generation of forest plot were carried out using Cochrane RevMan version 5.2 software (Cochrane Tech, London, UK).

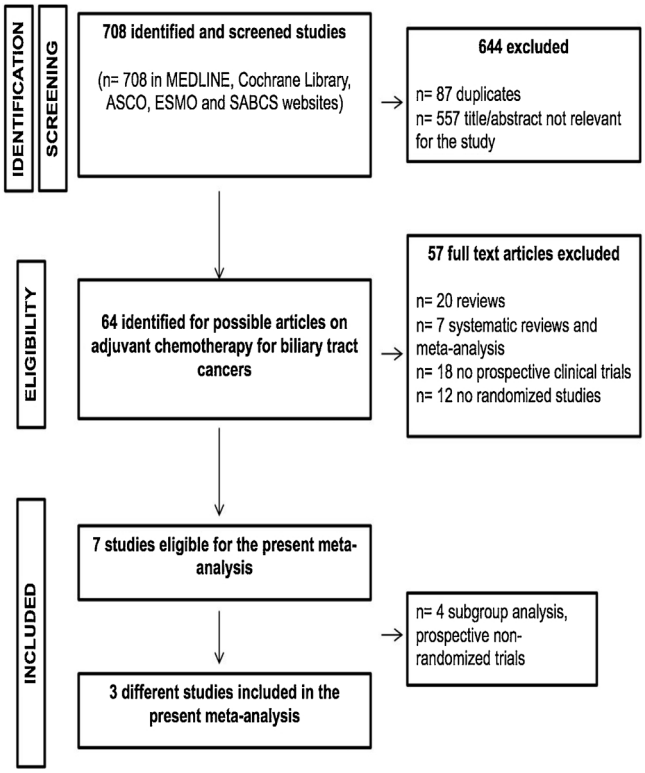

Fig. 1. The PRISMA flow chart summarizing the process for the identification of the eligible studies.

3. Results

The search strategy returned 708 records (Fig. 1): after the exclusion of 644 irrelevant publications, 64 were identified as records eligible for the present study. However, 57 full text records were excluded because did not fulfil all the prefixed eligibility criteria. Therefore, 7 records resulted eligible for our systematic review, but 4 were excluded because they were based on subgroup analysis or prospective non - randomized trials or have an active treatment in the control arm rather than observation (Kobayashi et al., 2019; Siebenhüner et al., 2018; Neoptolemos et al., 2012; Takada et al., 2002). Thus, we included and discussed three randomized phase III trials (Primrose et al., 2019; Edeline et al., 2019; Ebata et al., 2018) reporting data on the efficacy and safety of ACT versus observation alone. The adopted ACT was capecitabine in one trial (Primrose et al., 2019) and gemcitabine-based regimen in the remaining trials (Edeline et al., 2019; Ebata et al., 2018). A total of 866 resected BTC patients (ACT: 435, observation:431) were enrolled in the three trials. Patient characteristics were well balanced between study arms across trials (Table 1) and results were provided for the intention-to-treat population. Due to the lack of blinding of study participants and personnel all the three trials were considered 'at risk of bias', but this aspect was unlikely to influence the OS outcome. Risks of bias assessment are summarized in Table 2.

Table 1
Main characteristics of phase III randomized trials included in the present meta-analysis.

Trial	Design	Primary tumour site	Primary endpoint	R0 resection (%)	R1 resection (%)	Negative lymph nodes	Positive lymph nodes	OS (HR)	RFS (HR)	Toxicity G3/G4 in the experimental arm (≥2%)
BILCAP (Primrose et al., 2019)	Capecitabine vs observation	Intrahepatic, hilar and lower common bile duct cholangiocarcinoma, muscle-invasive gallbladder carcinoma	OS	62 experimental arm), 63 (control arm)	38 (experimental arm), 38 (control arm)	52 (experimental arm), 54 (control arm)	48 (experimental arm), 46 (control arm)	0.81 (95% CI 0.63–1.03, p = 0.097)	0.75 (95% CI 0.58–0.98 p = 0.033)	Hand-foot syndrome (20%), fatigue (8%), diarrhea (8%), gastrointestinal or abdominal pain (5%), neutrophil or granulocyte abnormality (2%)
PRODIGE (Edeline et al., 2019)	GEMOX vs observation	Intrahepatic, perihilar and distal cholangiocarcinoma, gallbladder carcinoma	RFS	86 (experimental arm), 88 (control arm)	14 (experimental arm), 12 (control arm)	52 (experimental arm), 48 (control arm)	37 (experimental arm), 36 (control arm)	1.08 (95% CI 0.70–1.66, p = 0.74)	0.88 (95% CI 0.62–1.25, p = 0.48)	Neutrophil decrease (17%), platelets decrease (7%), ALT increase (4%), AST increase (7%), alkaline phosphatase increase (9%), GGT increase (37%), peripheral sensory neuropathy (18%), diarrhea (4%), vomiting (2%), asthenia (8%)
BCAT (Ebata et al., 2018)	Gemcitabine vs observation	Perihilar and distal cholangiocarcinoma	OS	90.6 (experimental arm), 87 (control arm)	9.4 (experimental arm), 13 (control arm)	64.1 (experimental arm), 66.7 (control arm)	35.9 (experimental arm), 33.3 (control arm)	1.01 (95% CI 0.70–1.45, p = 0.964)	0.93 (95% CI 0.66–1.32, p = 0.693)	Leucocytes (29.2%), neutrophil (58.4%), hemoglobin (7.1%), platelets (7.1%) abnormality, fatigue (5.3%), anorexia (5.3%), fever (3.5%)

Legend: OS = overall survival, RFS = recurrence free survival, CI = confidence interval, HR = hazard ratio, GEMOX = gemcitabine plus oxaliplatin.

3.1. OS

The three phase III trials (Primrose et al., 2019; Edeline et al., 2019; Ebata et al., 2018) included in our systematic review assessed the OS benefit of ACT for resected BTC; hence results were suitable for the meta-analysis (Fig. 2). A total of 217 events occurred in 435 patients enrolled in the ACT arm and 229 in the 431 patients in the observation arm. The pooled HR was 0.91 (95% CI 0.75–1.09), indicating a 9% lower probability of developing death events among patients who received ACT compared with those who underwent surgery alone. However, the upper boundary limit of the confidence interval crosses the unit and the difference in terms of OS between ACT and observation alone was not statistically significant. Similarly, in the pre-specified subgroup analysis there was no effect of ACT on OS in ACT in N + subgroup (HR: 0.84, 95% CI 0.65–1.08) and in R1 subgroup (HR: 0.95 95% CI 0.69–1.31) (Fig. 3A and B).

No significant heterogeneity between the three studies was observed (I^2 0%) in both intention-to-treat and subgroup analysis.

3.2. RFS

The three phase III trials (Primrose et al., 2019; Edeline et al., 2019; Ebata et al., 2018) included in our systematic review assessed the RFS benefit of ACT versus observation alone: hence results were suitable for our meta-analysis (Fig. 4). A total of 256 events occurred in 435 patients enrolled in the ACT arm and 274 in 431 patients in the observation arm. A mild improvement in RFS (HR: 0.83, 95% CI 0.69–0.99) was reported among resected BTC patients treated with ACT. No significant heterogeneity between the three studies was observed (I^2 0%).

3.3. Toxicities

The three phase III trials (Primrose et al., 2019; Edeline et al., 2019; Ebata et al., 2018) included in our systematic review reported G3-G4 AEs occurring in the ACT arm and in the observation arm (Fig. 5).

A total of 183 resected BTC patients out of 435 (42%) treated with ACT developed G3-G4 AEs compared to 61 patients out of 431 (14%) assigned to observation arm. The pooled RR was 3.03 (95% CI 2.22–4.15), indicating a much higher probability of developing ≥ G3-G4 AEs for patients treated with ACT. A moderate heterogeneity between the three studies was observed (I^2 35%).

4. Discussion

Surgery represents the backbone and the only potential curative treatment of patients with localized BTC, offering the best chance of prolonging life expectancy (Khan et al., 2012). However, almost 50% of patients will experience disease recurrence after radical surgery and 5-year survival rate accounts for 10–40% (Komaya et al., 2018). R1 resection and N + disease represent the main two adverse prognostic features that correlate with early relapse and poor outcomes (Khan et al., 2012).

In the randomized phase III ABC-02 trial cisplatin and gemcitabine significantly improved OS compared to gemcitabine alone (HR 0.64, 95% CI 0.52–0.80) in patients with unresectable or metastatic BTC and now represents the standard of care in first line metastatic setting (Valle et al., 2010).

Accordingly, it was postulated that chemotherapy may prolong RFS and OS after radical resection in BTC patients.

Data concerning ACT are still controversial and there is no consensus by the majority of international guidelines about the optimal regimen to be used in this setting (Benson et al., 2009; Valle et al., 2016; Shroff et al., 2019).

A previous meta-analysis including mostly retrospective studies showed a potential OS benefit of ACT, particularly in patients with N +

Table 2
Risks of bias assessment of phase III randomized controlled trials included in the present meta-analysis.

Quality risk of bias (Higgins et al., 2011) Domain	BILCAP (Primrose et al., 2019)	PRODIGE (Edeline et al., 2019)	BCAT (Ebata et al., 2018)
Adequate sequence generatio	1:1 computer-generated randomization	1:1 computer-generated randomization	1:1 computer-generated randomization
	Stratification by surgical center, site of disease and performance status using a computerized minimization algorithm	Stratification by primary site, extent of resection, lymph node involvement and center using a minimization method	Stratification by residual tumor status, lymph node status, tumor location and enrolment center using a modified minimization method
Allocation concealment	Central allocation	Central allocation	Central allocation
Masking	Open-label design	Open-label design	Open-label design
Incomplete outcome data addressed	All randomized patients included in analyses	2 patients withdrawing consent in the experimental arm not included in the ITT analysis	All randomized patients included in analyses
Free of selective reporting	All outcomes of interest reported	All outcomes of interest reported	All outcomes of interest reported
Other quality assessment indicators (Higgins and Green, 2011)			
Indirectness	Survival rate higher than expected, possibly due to 'Fitness' of enrolled population (3% ECOG PS2) and centralization of surgical procedures	Fewer high-risk patients than average (R1 13%, N1 33%, gallbladder 17%)	Fewer high-risk patients than average (R1 11.1%, N1 34.7%, gallbladder 0%)
Inconsistency	Inconsistent findings with PRODIGE and BCAT trials Inconsistent findings for OS between ITT and per-protocol analysis	Inconsistent findings with BILCAP	Inconsistent findings with BILCAP
Imprecision	ITT OS HR 0.82 (0.63–1.04)	Wide CI for primary outcome RFS HR 0.88 (95% CI 0.62–1.25, p = 0.48)	Wide CI for outcomes OS HR 1.01 (95% CI 0.70–1.45, p = 0.964) RFS 0.93 (95% CI 0.66–1.32, p = 0.693) Possibly due to incomplete accrual of target sample size
Publication bias	Unlikely	Unlikely	Unlikely
Other sources of bias	- Population enriched for high risk patients (R1 35%, N + 54%, gallbladder 18%) - Long duration of accrual (March 2006–Dec 2014)	Median of 10 cycles with oxaliplatin delivered with only 33% of patients receiving the 12 planned cycles of GEMOX	- Incomplete accrual of estimated sample size (228 of 300 patients planned)

Legend: OS = overall survival, RFS = recurrence free survival, HR = hazard ratio, CI = confidence interval, ITT = intention-to-treat population, GEMOX = gemcitabine plus oxalipatin.

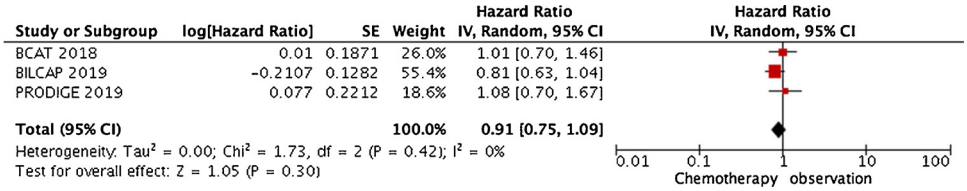

Fig. 2. Forest plot of hazard ratios (HRs) for overall survival (OS) in three randomized trials of adjuvant chemotherapy compared to observation alone for resected biliary tract cancers. Pooling HRs were computed using random-effect models. The bars indicate 95% confidence intervals.

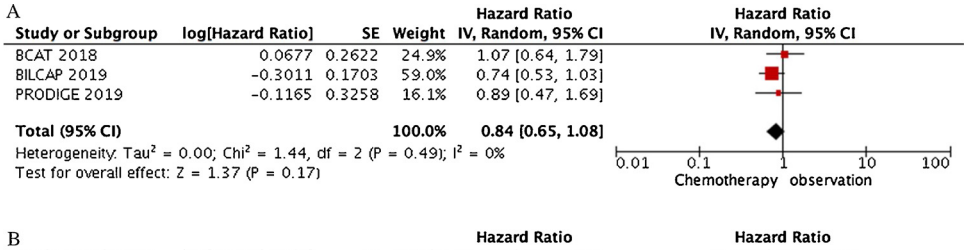

Fig. 3. Forest plot of hazard ratios (HRs) for overall survival (OS) in three randomized trials of adjuvant chemotherapy compared to observation alone for resected biliary tract cancers in node positive (**A**) and surgical margin positive (**B**) subgroups. Pooling HRs were computed using random-effect models. The bars indicate 95% confidence intervals.

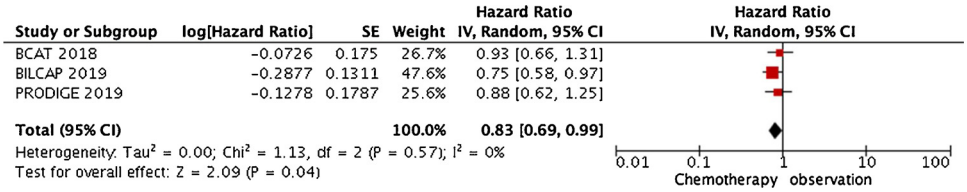

Fig. 4. Forest plot of hazard ratios (HRs) for recurrence free survival (RFS) in three randomized trials of adjuvant chemotherapy compared to observation alone for resected biliary tract cancers. Pooling HRs were computed using random-effect models. The bars indicate 95% confidence intervals.

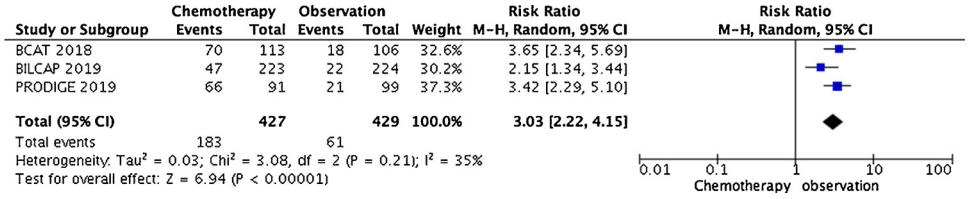

Fig. 5. Forest plot of risk ratios (RRs) for ≥ G3-G4 AE in three randomized trials of adjuvant chemotherapy compared to observation alone for resected biliary tract cancers. Pooling RRs were computed using random-effect models. The bars indicate 95% confidence intervals.

(OR 0.49, p = 0.004) and R1 disease (OR 0.36, p = 0.002) (Horgan et al., 2012). However, given the high heterogeneity of the studies included in the meta-analysis and the lack of evidence from randomized prospective trials, this finding was hypothesis generating.

A prospective randomized phase III trial failed to show an OS and RFS benefit of ACT in resected pancreaticobiliary cancers (Takada et al., 2002). However, this trial had several limitations concerning the long recruitment period (over 25 years) and the choice of the outdated regimen mitomycin C and 5-fluorouracil. Moreover, the inclusion of both pancreatic and biliary cancers limited the interpretation of trial findings.

Recently, three randomized phase III trial investigated the benefit and risks of ACT in resected BTC patients.

The BILCAP trial (Primrose et al., 2019) compared the efficacy of adjuvant capecitabine or observation in patients with resected BTC. Primary objective was OS. Although this trial failed to demonstrate an OS advantage in intention-to-treat population (HR 0.81, 95% CI 0.63–1.04), adjuvant capecitabine meaningfully improved OS in a protocol-specified sensitivity analysis (HR 0.71, 95% CI 0.55–0.92).

The PRODIGE 12-ACCORD 18 trial assessed the efficacy of adjuvant gemcitabine and oxaliplatin (GEMOX) or observation in resected BTC (Edeline et al., 2019). RFS was the primary end point.

There was no statistically significant difference in RFS between GEMOX and observation arm (HR 0.88, 95% CI 0.62–1.25) and OS was similar between the two groups (HR: 1.08, 95% CI 0.70–1.66).

Similarly, the randomized phase III BCAT trial evaluated the efficacy of adjuvant gemcitabine or observation in resected BTC (Ebata et al., 2018). OS was the primary endpoint. This trial suggested that adjuvant gemcitabine did not improve OS (HR 1.01, 95% CI 0.70–1.45) and RFS (HR 0.93, 0.66–1.32) compared to observation.

Our meta-analysis showed that ACT provides a mild benefit in terms of RFS (HR: 0.83, 95% CI 0.69–0.99) and no effect on OS in overall population (HR: 0.91, 95% CI 0.75–1.09) despite of higher risk of ≥ G3-G4 AEs (RR: 3.03, 95% CI 2.22–4.15).

Similarly, there was no effect of ACT on OS in N + subgroup (HR: 0.84, 95% CI 0.65–1.08). The lack of OS benefit in R1 patients is imprecise for the wide confidence interval (HR: 0.95 95% CI 0.69–1.31), reflecting the poor prognosis of this subgroup and highlighting the potential role of more intensive chemotherapy regimens or concomitant radiation in this setting. In the previous metanalysis a significant OS benefit for adjuvant radiation was found R1 subgroup (OR 0.33; 95% CI, 0.14 to 0.81; p = 0.01) while not for R0 (OR, 1.26;95%CI, 0.88–1.79; p = 0.20) (Horgan et al., 2012).

Several limitations of the present meta-analysis should be acknowledged; these include the lack of individual patient data (all data extracted from original articles), long recruitment period, differences in clinical trial design, heterogeneity in ACT regimens and patient's characteristics, different access to chemotherapy delivered after disease recurrence.

In terms of trial design, it is noteworthy that in contrast to the other two trials, PRODIGE 12-ACCORD 18 study had RFS as primary endpoint, thus it was probably underpowered to detect a gain in OS.

Moreover, different baseline characteristics were observed in the selected studies. BILCAP trial (Primrose et al., 2019) enrolled a higher proportion of patients with R1 (37%), N+ (47%) and gallbladder (18%) than in BCAT (11%, 34, 0%, respectively) or PRODIGE (13%, 37%, 20%, respectively). These findings suggest that the inclusion of patients with 'more' favourable prognostic factors in the two gemcitabine-based trials might have reduced the number of deaths events, negatively affecting the real benefit of ACT. Furthermore, our meta-analysis does not stratify patients according to BTC subtypes due to the high heterogeneity in cancer classification throughout the three trials. This may have skewed the results, particularly on the light of recent findings describing the mutational profile/landscape of BTC, that might refine BTC subtypes classification and improve treatment selection (Roos et al., 2019).

These limitations might have determined the upper limit of the confidence interval for the OS HR (95% CI 0.75–1.09), crossing the unit and missing statistically significance. Nonetheless, they do not substantially influence the overall interpretation of our findings, as are the result of a strict methodological analysis, which attempted to overcome the heterogeneity of available data. Our results add new potential insights on the efficacy and safety of ACT for resected BTC.

Results of ACTICCA-1 study (Clinical trial.gov NCT02170090) are still awaited to assess the efficacy of adjuvant gemcitabine plus cisplatin as ACT in radically resected BTC patients. Moreover, prospective evidences are needed to investigate the benefit and risks of concomitant radiotherapy to adjuvant chemotherapy rather than ACT alone.

5. Conclusion

To the best of our knowledge, this meta-analysis is the first attempt to investigate the efficacy and safety of ACT compared to observation alone based on data extracted from available published prospective randomized phase III trials. Our meta-analysis showed no effect of ACT on OS of resected BTC patients', a mild improvement in RFS and a substantial increase of chemotherapy-associated AEs. Therefore, in clinical practice clinicians should balance ACT benefits with higher toxicities treatment-related.

Disclosure statement

All authors declare no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

All the authors agree with this submission to Critical Reviews in Oncology/Haematology and have no conflicts of interest to declare. We confirm that this manuscript has not been published elsewhere and is not under consideration by any other journal.

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