Adjuvant chemotherapy in biliary tract cancer patients: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: The role of adjuvant chemotherapy in biliary tract cancer is controversial. We performed a systematic review and meta-analysis to assess the effect of adjuvant chemotherapy in biliary tract cancer patients.

Methods: A literature search was performed to identify randomized controlled trials (RCTs) comparing adjuvant chemotherapy versus observation, and a pooled analysis was conducted using the random-effect model.

Results: Three RCTs (N = 866) were included. No difference was observed between chemotherapy and observation in terms of OS (HR 0.91; 95%CI, 0.75–1.09; p = 0.295), whereas a significant improvement in RFS was shown (HR 0.83; 95%CI, 0.69–0.99; p = 0.040). No subgroup that benefited most from adjuvant chemotherapy was identified, although a trend was observed in N+ patients (HR 0.83; 95%CI, 0.65–1.08; p = 0.165).

Discussion: Adjuvant chemotherapy yields a significant RFS benefit in biliary tract cancer patients and should be considered for those who are able to tolerate additional treatment after surgery.

1. Introduction

The standard treatment of early-stage biliary tract cancer patients is surgery, which provides modest 5-year overall survival (OS) rates (10–40%) (Everhart and Ruhl, 2009; “RARECARENet - Information Network on Rare Cancers,” n.d.; Shaib and El-Serag, 2004). As an attempt to improve these outcomes, adjuvant chemotherapy has been administered for patients presenting high-risk features such as positive surgical margins (R1) and nodal involvement (N+), although these recommendations were based on retrospective series (Ghidini et al., 2017; Horgan et al., 2012; Mansour et al., 2015; Study Group of Surgical Adjuvant Therapy for Carcinomas of the Pancreas and Biliary Tract et al., 2002).

Two recent phase III trials that could not demonstrate the benefit of gemcitabine-based chemotherapy in biliary tract cancer patients have raised doubts about the role of adjuvant chemotherapy in this scenario (Ebata et al., 2018; Edeline et al., 2019). However, a third phase III study (BILCAP) evaluating adjuvant capecitabine in patients with resected biliary tract cancer brought new insights into this discussion: the intention-to-treat analysis for the study’s primary endpoint (OS) was negative (hazard ratio [HR] 0.81; 95% confidence interval [CI], 0.63–1.04; p = 0.097), although a clinically meaningful absolute improvement of 14.7 months in OS was observed with capecitabine. Moreover, a significant OS benefit with capecitabine was observed in a pre-planned sensitivity analysis adjusted for prognostic factors (HR 0.75; 95%CI, 0.58–0.97; p = 0.010) and in the per-protocol analysis (HR 0.75; 95%CI, 0.58–0.97; p = 0.028). Recurrence-free survival (RFS) was also significantly improved with capecitabine (median RFS 24.4 months versus 17.5 months, HR 0.75; 95%CI, 0.58–0.98; p = 0.033) (Primrose et al., 2019).
The absolute OS improvement yielded by chemotherapy in the BILCAP study has motivated the incorporation of adjuvant capecitabine as the new standard treatment for biliary tract cancer patients in international guidelines (Shroff et al., 2019). However, considering that 2 previous phase III studies did not demonstrate any benefit with the administration of adjuvant chemotherapy in biliary tract cancer patients, the role of this strategy remains debatable. Aiming to provide updated data into this controversial topic, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing adjuvant chemotherapy versus observation in patients with non-metastatic biliary tract cancer.

2. Materials and methods

This is a quantitative synthesis and meta-analysis based on published or publically available data including RCTs comparing systemic chemotherapy versus observation in the adjuvant treatment of biliary tract cancer patients.

2.1. Objectives

The objective of this meta-analysis was to compare adjuvant chemotherapy versus observation in biliary tract cancer patients, for the endpoints of OS and RFS. OS was defined as the time from randomization to death; RFS was defined as the time from randomization to disease-recurrence or death, whichever occurred first.

Subgroup analyses to evaluate treatment effect according to lymph node status (N0 [no lymph nodes involved] and N+ [≥ 1 lymph node involved]), surgical margins (R0 [negative] and R1 [positive], and primary tumor location (extrahepatic, intrahepatic and gallbladder) are secondary objectives.

2.2. Data sources and search strategy

A literature search in PubMed, EMBASE, the Cochrane Library, and conference proceedings from the annual meetings of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) was performed with no date restriction up to June 10, 2019. The search strategy was developed using the patient, intervention, comparator and outcome (PICO) framework and comprised the keywords related to “biliary tract cancer” and “adjuvant chemotherapy”. Specific keywords for each database and texts were combined with appropriate Boolean operators. The most adequate combination of terms was designed by one reviewer (RC) and approved by other two reviewers (GEH and AH) according to each database’s specific criteria. Two reviewers (RC and GEH) independently evaluated the titles and the abstracts of the identified studies to apply eligibility criteria; a third author (AH) was consulted in case of discrepancies. Cross-referencing from relevant studies and review articles on the topic was performed to confirm that all eligible trials were included. More information on the search strategy used in one of the databases (PubMed) is available as Supplementary material. This research was conducted and reported according to the PRISMA guidelines for systematic reviews, and registered at PROSPERO database (CRD42018110297; full protocol available in the website) (Moher et al., 2009).

2.3. Records’ selection

Eligible studies had to meet the following inclusion criteria: RCTs with published, presented or otherwise publically available data; including only biliary tract cancer patients; comparing systemic (intravenous or oral) chemotherapy (any regimen, any duration) versus observation; having available information regarding the endpoints of the present meta-analysis; only publications in English were considered.

Excluded studies were RCTs including patients with other tumors
besides biliary tract cancer (pancreatic, [peri]ampullary, duodenal) and not reporting the respective HR for RFS/OS for the biliary tract cancer subgroup; studies evaluating non-systemic chemotherapy (intra-hepatic, intraperitoneal or intra-gallbladder), chemoradiation or radiation alone as adjuvant treatments; non-randomized and non-prospective studies; studies for which insufficient or no results where available.

### 2.4. Statistical analysis

Unadjusted HRs from the intention-to-treat analysis of each study were extracted, and HRs were calculated for the comparison of chemotherapy versus observation. A HR < 1 favours chemotherapy (i.e. longer OS/RFS with chemotherapy), whilst a HR > 1 favours observation (i.e. longer OS/RFS with observation). Pooled HRs using the random-effects model was computed with the method of DerSimonian and Laird. The Higgins’ $I^2$ index was computed to obtain a quantitative measure of the degree of inconsistency in the results of the studies included. All p-values were two-sided. To assess whether the pooled HR estimates were stable or strongly dependent on one of the studies included, sensitivity analyses were conducted by interactively recalculating the pooled HR estimates after exclusion of each single study.

All statistical analyses and the generation of forest plots were carried out using Stata Software Version 13.1 (StataCorp LP). The Cochrane risk of bias assessment tool was employed to assess the quality of the data and the risk of bias in each of the RCTs (Supplementary material, Table 1) (Higgins et al., 2011).

### 3. Results

The literature search identified 258 records. After the exclusion of 237 records considered not relevant to the research question or duplicates, 21 potentially eligible studies were identified. Of these, 16 were not RCTs, and 2 enrolled patients with tumors other than biliary tract cancer (and did not report a separate HR for the subgroup of biliary tract cancer). Hence, 3 RCTs were included (BCAT, BILCAP and PRODIGE) comprising a total of 866 patients (Ebata et al., 2018; Edeline et al., 2019; Primrose et al., 2019) (Fig. 1).

In the chemotherapy arm of all the included RCTs, patients received systemic adjuvant chemotherapy, whilst in the observation arm patients were treated with surgery alone. In all the RCTs, patients were followed after surgery with regular laboratory and imaging exams. In the BILCAP and BCAT studies, the primary endpoint was OS, whereas PRODIGE had RFS and quality of life as co-primary endpoints. Table 1 illustrates the characteristics of the RCTs included.

#### 3.1. Overall survival

All studies reported OS results, with 217 events amongst 435 patients in the chemotherapy group and 229 events amongst 431 patients in the observation group. No significant difference was observed between chemotherapy and observation in terms of OS (HR 0.91; 95%CI, 0.75–1.09; $p = 0.295$) with no significant heterogeneity ($I^2 = 0$%; $p_{\text{heterogeneity}} = 0.418$; Fig. 2A). Sensitivity analysis is reported as Supplementary material, Table 2A.

#### 3.2. Relapse-free survival

All studies reported RFS results, with a total of 256 events amongst 435 patients in the chemotherapy group and 274 events amongst 431 patients in the observation group. A significant improvement in terms of RFS was observed with chemotherapy in comparison to observation (HR 0.83; 95%CI, 0.69–0.99; $p = 0.040$) with no significant heterogeneity ($I^2 = 0$% ; $p_{\text{heterogeneity}} = 0.579$; Fig. 2B). Sensitivity analysis is reported as Supplementary material, Table 2B.

#### 3.3. Subgroup analysis

##### 3.3.1. Lymph node status

All studies reported OS results according to lymph node status. In N0 patients ($N = 480$), no significant difference was observed between chemotherapy and observation (HR 0.92; 95%CI, 0.69–1.22; $p = 0.555$) with no significant heterogeneity ($I^2 = 0$ %; $p_{\text{heterogeneity}} = 0.528$; Fig. 3A). In N + patients ($N = 359$), no significant difference was observed between chemotherapy and observation (HR 0.83; 95%CI, 0.65–1.08; $p = 0.165$) with no significant heterogeneity ($I^2 = 0.0$ %; $p_{\text{heterogeneity}} = 0.489$; Fig. 3B). Sensitivity analysis is reported as
3.4. Surgical margins

All studies reported OS results according to surgical margins status. In R0 patients (N = 648), no significant difference was observed between chemotherapy and observation (HR 0.88; 95 %CI, 0.69–1.10; p = 0.224), with no significant heterogeneity (I² = 0.0 %; p heterogeneity = 0.417; Fig. 4A). In R1 patients (N = 218), no significant difference was observed between chemotherapy and observation (HR 0.95; 95 %CI, 0.69–1.31; p = 0.768), with no significant heterogeneity (I² = 0 %; p heterogeneity = 0.789; Fig. 4B). Sensitivity analysis is reported as Supplementary material, Table 4.

3.5. Primary tumor

Two studies (BILCAP and PRODIGE) reported OS results according to primary tumor, whereas the BCAT study enrolled exclusively patients with extrahepatic tumors. In BILCAP, the extrahepatic subgroup was divided between “hilar” and “common bile duct”; we chose to extract data from the common bile duct subgroup, due to its largest sample size.

3.6. Extrahepatic tumors

All studies reported OS results in patients with extrahepatic tumors (N = 579). No significant difference was observed between chemotherapy and observation (HR 0.84; 95 %CI, 0.65–1.08; p = 0.169), with no significant heterogeneity (I² = 0 %; p heterogeneity = 0.368; Fig. 5A). Sensitivity analysis is reported as Supplementary material, Table 5.

3.7. Intrahepatic tumors

Two studies (BILCAP and PRODIGE) reported OS results in patients with intrahepatic tumors (N = 170). No significant difference was observed between chemotherapy and observation (HR 0.77; 95 %CI, 0.49–1.20; p = 0.243), with no significant heterogeneity (I² = 0 %; p heterogeneity = 0.433; Fig. 5B).

3.8. Gallbladder tumors

Two studies (BILCAP and PRODIGE) reported OS results in patients with gallbladder tumors (N = 117). No significant difference was observed between chemotherapy and observation (HR 1.58; 95 %CI, 0.41–6.17; p = 0.509), with significant heterogeneity between studies.
4. Discussion

The present meta-analysis reports updated evidence on the impact of adjuvant chemotherapy in biliary tract cancer patients. By pooling results from 3 RCTs and a total of 866 patients, we observed a significant benefit of adjuvant chemotherapy in terms of RFS, although no OS benefit was shown. No subgroup in which the benefit of chemotherapy was more pronounced was identified, although a trend in N+ patients was observed.

A 2012 meta-analysis (20 studies; N = 6,712) did not demonstrate an OS benefit with adjuvant treatment compared to observation in biliary tract cancer patients (Odds ratio [OR] 0.74; 95 %CI, 0.55–1.01; p = 0.06), however a significant OS benefit in N+ (OR 0.49; 95 %CI, 0.30–0.80; p = 0.004) and R1 (OR 0.36; 95 %CI, 0.19–0.68; p = 0.002) patients was observed. Although this meta-analysis suggests that adjuvant treatment benefits patients with high-risk features, studies evaluating different strategies (chemotherapy, concurrent chemoradiation and radiotherapy) were included, of which 1 out of 20 was a RCT, therefore an adequate evaluation of adjuvant chemotherapy was precluded (Horgan et al., 2012). A more recent meta-analysis (30 studies; N = 22,499) demonstrated a significant OS benefit for adjuvant treatment versus observation in biliary tract cancer patients (HR 0.59; 95 %CI, 0.49–0.71; p < 0.001) (Ghidini et al., 2017). However, the same methodological issues were present: only 1 out of the 30 studies was a RCT, and the adjuvant group comprised heterogeneous treatments, limiting the interpretation of its results, and highlighting the importance of performing an updated meta-analysis including only RCTs.

Even though the BILCAP study was negative for its primary endpoint, a clinically relevant absolute improvement of 14.7 months in OS was observed with adjuvant capecitabine. Notably, in the PRODIGE study a non-significant although meaningful absolute improvement in median OS was also observed with chemotherapy (75.8 months versus 50.8 months; HR 1.08; 95 %CI, 0.70–1.66; p = 0.74) (Edeline et al., 2019). Based on the fact that the per-protocol, the sensitivity and the RFS analyses of the BILCAP study were positive, capecitabine was incorporated in international guidelines as the new standard adjuvant treatment for biliary tract cancer patients (Primrose et al., 2019; Shroff et al., 2019). By demonstrating a significant RFS benefit with adjuvant chemotherapy, our meta-analysis supports the BILCAP results and the

![Forest plots and pooled hazard ratios with respective p values for overall survival in N0 (A) and N+ (B) patients.](image-url)
ASCO guidelines (Malka and Edeline, 2019; Primrose et al., 2019; Shroff et al., 2019).

Patients enrolled in the BILCAP study had a higher frequency of high risk features (N + and R1) in comparison to the population from PRODIGE and BCAT studies. As a consequence, recurrence rates were higher in BILCAP when compared to BCAT and PRODIGE studies (Ebata et al., 2018; Edeline et al., 2019; Primrose et al., 2019) (Supplementary Material, Table 6). Assuming that high-risk patients derive more benefit from adjuvant treatment, a more robust effect of chemotherapy should be expected in the population enrolled in the BILCAP study (Horgan et al., 2012). Also, potential differences between the effectiveness of the chemotherapy regimens of each study may have influenced the results (Abdel-Rahman et al., 2018; Ghidini et al., 2018; Valle et al., 2010). Notably, the genomic profile of biliary tract cancer varies significantly according to the primary tumor location, which may ultimately influence the prognosis and the chemotherapy sensitivity of the patients enrolled in each RCT (Verlingue et al., 2017).

The choice between OS or RFS as the primary endpoint of studies evaluating adjuvant chemotherapy in biliary tract cancer is debatable, provided the OS benefit yielded by cisplatin and gemcitabine in the metastatic setting (Valle et al., 2010). While subsequent treatments were not reported in BILCAP, gemcitabine-based chemotherapy was administered after relapse to 98 % of the patients in the observation arm versus 27 % in the chemotherapy arm in the PRODIGE study (Edeline et al., 2019). Ultimately, more patients may have received cisplatin and gemcitabine as first-line treatment of metastatic disease in BILCAP (capecitabine-based adjuvant treatment) in comparison to PRODIGE and BCAT (gemcitabine-based adjuvant treatment) (Ebata et al., 2018; Edeline et al., 2019; Primrose et al., 2019). Interestingly, in BILCAP the RFS benefit was significant in the first 2 years (HR 0.75; 95 %CI, 0.58-0.98; p = 0.033), but not sustained from years 2 to 5 (HR 1.48; 95 %CI, 0.80-2.77; p = 0.21) (Primrose et al., 2019). Indeed, in BILCAP the impact of adjuvant chemotherapy was more pronounced in RFS than in OS, and in the PRODIGE study post-relapse survival tended to be higher in the observation arm in comparison to the chemotherapy arm (15.2 versus 8 months; HR 1.55; 95 %CI, 0.98-2.47; p = 0.06), suggesting that subsequent lines might have influenced patients’ outcomes (Edeline et al., 2019; Primrose et al., 2019). The mature OS data of these studies should help clarifying this point. As for today, we cannot exclude the hypothesis that adjuvant chemotherapy only delays recurrence with a limited impact on OS.

The primary endpoint of the BILCAP and the BCAT studies was OS,
A – Overall survival in patients with extrahepatic tumors

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Year</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCAT</td>
<td>2018</td>
<td>1.01 (0.70, 1.45)</td>
</tr>
<tr>
<td>BILCAP</td>
<td>2019</td>
<td>0.70 (0.47, 1.06)</td>
</tr>
<tr>
<td>PRODIGE</td>
<td>2019</td>
<td>0.70 (0.34, 1.44)</td>
</tr>
</tbody>
</table>

Random effect: $p=0.169$

B – Overall survival in patients with intrahepatic tumors

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Year</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BILCAP</td>
<td>2019</td>
<td>0.65 (0.35, 1.18)</td>
</tr>
<tr>
<td>PRODIGE</td>
<td>2019</td>
<td>0.93 (0.48, 1.79)</td>
</tr>
</tbody>
</table>

Random effect: $p=0.243$

C – Overall survival in patients with gallbladder tumors

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Year</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BILCAP</td>
<td>2019</td>
<td>0.84 (0.43, 1.63)</td>
</tr>
<tr>
<td>PRODIGE</td>
<td>2019</td>
<td>3.39 (1.17, 9.83)</td>
</tr>
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Random effect: $p=0.509$

Fig. 5. Forest plots and the pooled hazard ratios with the respective $p$ values for overall survival in patients with extrahepatic (A), intrahepatic (B) and gallbladder (C) primary tumors.
whereas in PRODIGE it was RFS. In the statistical design of the PRODIGE study, the estimated benefit of adjuvant chemotherapy was ambitious (HR of 0.6 expected), leading to a small sample size and an ultimately underpowered study. In the BCAT trial, the 5-year survival rate in the observation arm was around 50 %, higher than the expected 30 %. The same discrepancy was observed in BILCAP, since the 2-year survival rate of 60 % in the observation arm was higher than the expected 20 %. The higher-than-anticipated survival rates in the observation arms of these studies suggest that the surgical techniques and the post-operative care of biliary tract cancer patients are evolving, and the lower-than-expected number of events has affected the studies' power to assess survival differences (Malka and Edeline, 2019; Nagino et al., 2013).

Although the 14.7-month OS benefit observed in BILCAP was considered clinically meaningful, it did not reach statistical significance (Primrose et al., 2019). The lack of statistical significance may have occurred due to higher than expected survival rates observed in patients from the control arm, which reduced the statistical power of the OS analysis. Historical survival rates of biliary tract cancer patients served as a basis for the statistical assumptions performed in BILCAP. Notably, the increment in OS yielded by contemporary surgical and post-operative treatments was difficult to be anticipated at the time the study was conceived. In this context, the survival data generated by contemporary RCTs will contribute to improve statistical assumptions for future studies. In the era of evidence-based medicine, statistically positive results from clinical trials are important to support medical decisions (Evidence-Based Medicine Working Group, 1992). However, the adequate interpretation of studies’ results, together with an evaluation of the risks and benefits that an intervention may present for each patient, are also important factors taking part in the complex decision making process in medical oncology. As an example, the addition of erlotinib to gemcitabine in metastatic pancreatic cancer patients yielded a 0.3 month improvement in OS in a randomized phase III study (Moore et al., 2007). Although this benefit was statistically significant (p = 0.038), its clinical relevance is questionable (Miksad et al., 2007). Indeed, the fact that biliary tract cancer is a highly lethal disease, for which treatment options are scarce, contributed to enhance the clinical relevance of the BILCAP study results (Patel, 2001).

Potential limitations have to be considered when interpreting our findings: the data were not individual-patient level; each RCT used a different chemotherapy regimen; and no long-term follow-up is available for 2 out of the 3 RCTs included, affecting the OS assessment (Ebata et al., 2017; Ramirez-Merino, 2013; Valle et al., 2010). Subgroup analyses of RFS were not performed due to the absence of this data in the BILCAP study. (11) An additional per-protocol analysis of RFS and OS was not performed due to the absence of this data in the BCAT study (Ebata et al., 2018). Data was unavailable in two RCTs to perform subgroup analysis of OS according to tumor grade and gender. (9,10) Nevertheless, this meta-analysis included only RCTs comparing systemic chemotherapy versus observation, providing updated evidence on the effect of adjuvant chemotherapy in biliary tract cancer patients.

In conclusion, our meta-analysis demonstrated that adjuvant chemotherapy yields a significant RFS benefit in biliary tract cancer patients, supporting the ASCO guidelines that recommend this strategy for patients who are able to tolerate additional treatment after surgery (Primrose et al., 2019; Shroff et al., 2019). A longer follow-up of the included RCTs and the results of ongoing studies (UMIN000011688, NCT02170090) may clarify if the RFS benefit observed with adjuvant chemotherapy will translate into an OS benefit. The incorporation of tumor genomic profile as a stratification factor in future studies should contribute to identify patients who benefit from adjuvant chemotherapy.

Authors’ contributions
RC, GEH and AH have conceived this research project. RC and GEH have performed the literature search. MB and MC have performed the statistical analysis. All authors have participated in the discussion of the manuscript, and all authors have reviewed the final version of this manuscript before submission.

Ethical approval and consent to participate
The present manuscript did not perform any experiments with human subjects, and no ethical approval was necessary.

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Appendix A. Supplementary data
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References


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