



Adjuvant treatment in biliary tract cancer

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Abstract: Biliary tract cancers (BTCs) are a heterogeneous group of malignancies with a dismal prognosis. Despite radical surgery, the five-year overall survival (OS) does not exceed 40% in the best series. Adjuvant treatments are widely used even though they have mainly been investigated in small retrospective series until recently. Available data suggest that chemotherapy with 5-fluorouracil (and relative prodrugs) or gemcitabine can reduce the risk of relapse and potentially improve patients' long-term outcome. The role of adjuvant radiotherapy seems to be confined to patients with positive surgical margins. In addition, patients with high-risk factors for relapse (nodal involvement and non-radical resection) benefit most from chemotherapy. Recent results from large randomized trials have clarified the benefit of adjuvant treatments and probably defined a new standard of care.

Keywords: Biliary tract cancer (BTC); adjuvant treatment; prognostic factors; chemotherapy; radiotherapy

Submitted Aug 04, 2018. Accepted for publication Aug 12, 2018.

doi: 10.21037/tcr.2018.08.17

View this article at: <http://dx.doi.org/10.21037/tcr.2018.08.17>

Introduction

Biliary tract cancers (BTC) comprise a heterogeneous group of malignancies arising along the biliary tree with a low incidence and poor prognosis. BTC account for nearly 3% of all gastrointestinal cancers (1) and are classified according to anatomical location into intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma, also known as Klatskin tumor (pCCA) and distal extrahepatic cholangiocarcinoma (eCCA). Despite having a different biological behavior and prognosis, ampullary and gallbladder cancers are grouped with cholangiocarcinoma (CCA) in some series.

Radical surgery is the only available treatment with curative intent. Five-year survival rates range from 20% to 32% for iCCA, 30% to 42% for pCCA and from 18% to 54% for eCCA (2). Unfortunately, only a minority of patients (20–30%) are diagnosed with early resectable disease and the rate of recurrence is high (2). In addition, the effectiveness and modalities of laboratory/instrumental

follow-up after surgery remain unclear.

Some series explored the feasibility of liver transplantation (LT) on early iCCA and pCCA (in the latter case after neoadjuvant radiochemotherapy). Overall LT is not readily available and its effectiveness, especially in iCCA patients, remains controversial (3,4).

The rationale for adjuvant treatment after surgery is to reduce the risk of relapse and improve the long-term outcome of resected patients. However, few high quality data on adjuvant treatments in BTC patients have been published to date. A combination of cisplatin and gemcitabine is the standard first-line chemotherapy (CTX) regimen in patients with advanced BTC. No standard second-line treatment has been established to date. Several clinical trials of therapies targeted against new actionable mutations (such as IDH1/IDH2 mutations and FGFR-2 fusion proteins) are now ongoing (5). This paper summarizes the available data and clinical evidence, and discusses the main open questions on adjuvant strategies in resected BTC patients.

Prognostic factors after surgery

Considering that less than one third of patients with CCA undergo a potentially curative resection and the disease has a high relapse rate, the identification of negative prognostic factors may serve to select a group of patients who could benefit most from adjuvant treatments.

The overall survival (OS) of patients who undergo surgical resection with curative intent varies according to pathological stage (6). A recent retrospective multi-institutional analysis evaluated the prognostic accuracy of the latest AJCC staging system (7) in patients with iCCA, showing that 5-year OS for patients classified as stages Ia, Ib, II, IIIa and IIIb was 90.0%, 50.6%, 55.1%, 49.7% and 16.2%, respectively (8). According to the results of a retrospective analysis of surgical series, the main prognostic factors associated with survival and risk of relapse in resected CCA patients are lymph node involvement and histologic margin status for both intrahepatic and extrahepatic forms. DeOliveira and colleagues' retrospective mono-institutional series found surgical margin status ($P<0.001$), lymph node status ($P<0.001$) and tumor differentiation ($P<0.001$) independent prognostic factors at both univariate and multivariate analysis. Moreover, among R0-resected patients, only nodal status was significantly associated with survival (HR 1.73, 95% CI: 1.26–2.39; $P<0.001$) (9).

The role of lymphadenectomy in the surgical treatment of iCCA is controversial. Uchiyama *et al.* reported that pathological lymph node involvement was significantly associated with poor survival (HR 2.10, $P<0.001$) in patients treated with radical resection for iCCA, while a high preoperative CA 19.9 (>135 U/mL) was the only significant factor predicting the risk of nodal involvement (10). A retrospective multicenter Italian study on 430 patients who underwent potentially curative resection for iCCA showed that lymph node metastasis was the most relevant independent predictor of poor survival (HR 2.21, 95% CI: 1.55–3.15; $P=0.005$), followed by elevated preoperative CA 19-9 levels (HR 1.62, $P=0.006$) and multiple tumors (HR 1.50, $P<0.001$) (11). Several studies showed that the ratio between the number of positive lymph nodes and the number of total lymph nodes examined is an independent prognostic factor for both OS and recurrence-free survival (RFS) in resected BTC (12). In de Jong *et al.*'s series of 449 patients with resected iCCA, vascular invasion and multiple tumors were significantly associated with poor prognosis. Lymph node involvement (N1) in the subgroup of patients who received lymphadenectomy ($n=248$) was associated with worse survival

than node-negative (N0) status (mOS 22.9 *vs.* 30.1 months, respectively, $P=0.03$) (13). Moreover, tumor number and vascular invasion significantly influenced prognosis only in N0-patients ($P=0.004$ and $P=0.009$, respectively), whereas these factors did not affect the survival of patients with node-positive disease ($P=0.45$ and $P=0.30$, respectively) (13).

Together with lymph node status, the other main factor most influencing the outcome of patients treated with radical-intent surgery for BTC is the histologic margin status. A French multicenter study on 212 patients treated with potentially curative resection for iCCA showed that a positive surgical margin at microscopic pathological examination (R1) was significantly associated with lower survival only among patients without lymph node metastases (N0). In the group of N+ patients, OS after R1 and R0 resection was similar (14). A retrospective analysis of patients with pCCA treated at Memorial Sloan-Kettering Cancer Center over a nine-year period revealed that survival after R0 resections was significantly longer than after R1 resections (42 *vs.* 21 months; $P<0.008$) (15). Uchiyama *et al.* showed that positive resection margins significantly reduced OS (HR 1.81; $P<0.006$) at multivariate analysis in patients with iCCA who underwent surgical resection with curative intent (10).

For perihilar BTC, an aggressive surgical approach with the addition of a major hepatectomy and a complete caudate lobectomy to bile duct resection has improved resectability rates in recent years (16). A multicenter Italian study on 440 consecutive patients with resected pCCA showed that aggressive surgical treatment significantly increased median OS without a concomitant increase in perioperative mortality. Lymph node metastases, R1 resection and T stage ≥ 3 were independent prognostic factors for OS and disease-free survival (DFS) at multivariate analysis (17). The prognostic role of other factors such as histological subtype, vascular invasion or preoperative CA 19-9 levels in patients with resected CCA has been studied but their importance in predicting survival and risk of recurrence is controversial (2,9,18).

In recent years, some authors have proposed different prognostic nomograms to better predict survival after potentially curative surgery. For instance, a prognostic model based on nodal involvement, tumor differentiation, and margin status in resected pCCA patients was proposed by Groot Koerkamp *et al.* (19). Furthermore, the prognostic nomogram for resectable iCCA proposed by Wang *et al.* included lymph node status, vascular invasion, tumor diameter and number and serum CEA and CA 19-9 levels, proving more accurate in predicting survival compared to traditional staging systems. Further studies are required for their validation (20).

Adjuvant treatments

Five-year OS after surgical resection does not exceed 40% in the best surgical series. Disease relapse occurs mainly during the first 2 years. Improving the outcome of surgery with adjuvant medical strategies is a major goal, not fully achieved to date. Attempts to solve this issue have to tackle considerable problems. Firstly, BTC is rare and few patients undergo surgery. Hence, it is arduous to design and finalize a randomized adjuvant trial with adequate statistical power. Secondly, BTC is a heterogeneous disease harboring different molecular and biological features (21). Finally, until some years ago there was no worldwide consensus on the standard CTX regimen also in a metastatic setting. Consequently, many adjuvant treatments and regimens have been explored in small uncontrolled mono-institutional series without a solid background in advanced disease. Despite the lack of strong definitive agreement, adjuvant CTX is widely employed at least in referral centers. Its use in clinical practice is suggested by guidelines and consensus statements, especially for patients with node-positive or margin-positive disease.

Hereafter, the main published or ongoing studies focused on adjuvant CTX, radiotherapy (RT) and chemoradiotherapy are reported.

Chemotherapy

Data are available from four prospective trials.

ESPAC-3

This was a three-arm international randomized trial in patients with resected periampullary malignancies (297 ampullary, 96 bile duct, 35 other). Overall, 428 patients were enlisted and randomized to observation (145 pts), 6 months of leucovorin-modulated 5-fluorouracil (FU) (143 pts) or six months of single-agent gemcitabine (146 pts). The primary end-point was OS in the treatment group compared to the observation group. Secondary end-points were disease-free survival, toxicities and quality of life. Adjuvant CTX provided a potential OS benefit even if it was not statistically significant (mOS 43 *vs.* 35 mo, HR 0.86, 95% CI: 0.66–1.11). A pre-planned subset analysis of BTC patients (96 pts) reported a mOS of 27, 18, and 20 months in observation, FU/leucovorin and gemcitabine, respectively. Near to 20% of patients in the 5-FU arm did not start the therapy and only 49% of them completed all pre-planned cycles. Likewise, in the gemcitabine arm, 11% of patients did not start the therapy and only 50% of them completed all the planned cycles (22).

JSGSAT study

This Japanese study enrolled 508 patients (between 1986 and 1992) with resected pancreatic (n=173), bile duct (n=139), gallbladder (n=140), or ampulla of Vater (n=56) cancers. Patients were randomly assigned to adjuvant CTX (mitomycin and 5-FU) or observation alone until disease recurrence. The treatment started on the day of surgery and ended once the patient developed recurrence. The treatment completion rate was high (>80%). No significant differences in 5-year OS or 5-year DFS rates were reported between patients with pancreatic, bile duct, or ampulla of Vater cancers. Multivariate analyses showed a non-significant lower risk of mortality (risk ratio of 0.654; *P*=0.0825) and recurrence (risk ratio of 0.626; *P*=0.0589) in the CTX group. Adjuvant CTX improved the five-year OS (26% *vs.* 14.4%, *P*=0.03) and DFS (20.3% *vs.* 11.6%, *P*=0.02) in the gallbladder subgroup with respect to observation alone, but only in the cases of non-curative resection. There are no definitive explanations for the reported differences (23).

PRODIGE 12-ACCORD 18

This French study, presented at the ASCO Gastrointestinal Cancers Symposium 2017, is a randomized study that compared an adjuvant treatment based on GEMOX to surgery alone in 193 patients who underwent R0 or R1 resections for BTC (24). A pathological involvement of the regional lymph nodes (pN1) was reported in about a third of cases and microscopic residual disease (R1) in about 13% of patients. At a median follow-up of 44.3 months, there were no significant differences in terms of RFS between the two arms (mRFS 30.4 months for the CTX arm *vs.* 22.0 months for the control arm, HR 0.83, 95% CI: 0.58–1.19; *P*=0.31) (24). Final RFS and first OS analysis, presented at ESMO 2017 Congress, confirmed the lack of benefit (25).

BILCAP

This was a randomized multicenter phase III trial from the UK evaluating the role of adjuvant CTX with capecitabine following potentially curative resection of CCA. The study randomized 447 patients with completely resected CCA or gallbladder cancer to either adjuvant CTX with capecitabine (1,250 mg/mq D1–D14 every 21 days, for 8 cycles) or observation. The preliminary results of the study were presented at the 2017 ASCO Annual Meeting. According to the intention-to-treat analysis, median OS was 36.4 months in the group of patients treated with surgery alone and 51.1 months in the adjuvant CTX arm (HR 0.81, 95% CI: 0.63–1.04) although the difference was not statistically significant (*P*=0.097). By per-

protocol analysis on 430 patients, excluding those who stopped capecitabine early, adjuvant CTX significantly improved survival compared to surgery alone (mOS 53 *vs.* 36 months, respectively; HR 0.75, $P=0.028$). In addition, sensitivity analyses with adjustment for clinical and pathological parameters such as nodal status, tumor grade, and gender showed a significant survival benefit in favor of capecitabine (HR 0.70, 95% CI: 0.55–0.91; $P=0.007$) (26). Based on these results, CTX with capecitabine will potentially become the new standard of care for adjuvant treatment in patients with BTC.

Radiotherapy and chemoradiotherapy

The role of adjuvant RT alone was evaluated in only one prospective, no-randomized trial at Johns Hopkins Hospital from 1988 to 1993 (27). Pitt *et al.* enlisted 50 non-metastatic CCA patients who underwent radical and non-radical resections or palliative surgery. Patients were treated or not with RT and stratified by tumor resection and other parameters that might have affected their outcome. RT did not improve survival either in resectable or in unresectable patients.

The role of adjuvant chemoradiotherapy was assessed by the studies summarized below.

EORTC

This was a small two-arm randomized trial which included 207 patients with pancreatic or periampullary malignancies (75–80% of R0 resection). A postoperative fluoropyrimidine-based chemoradiotherapy (total absorbed dose of 40 Gy and concomitant radio-sensitizing 5-FU) was compared to surgery alone. Patients enrolled in the combination arm were treated for a total of six weeks, including the two weeks of rest between the first and the second course of chemoradiotherapy. The trial failed to show a benefit in OS or progression-free survival, but fewer than 100 patients had periampullary malignancies and even fewer distal BTC. Furthermore, the dropout rate in the treatment arm was 20% due to postoperative complications or refusal.

SWOG S0809

The SWOG S0809 was a single arm prospective phase II trial of adjuvant combination CTX (capecitabine plus gemcitabine) followed by RT and concurrent capecitabine in eCCA and gallbladder cancer. Overall treatment lasted from 18 to 19 weeks. Patients received four cycles of CTX (12 weeks) and 5 to 6 weeks of chemoradiotherapy (starting in the thirteenth week). Seventy-nine eligible patients were treated. Eligibility criteria were pT2–T4 disease, node-

positive disease or R1 resection. Two-year OS and DFS were 65% and 52%, respectively. Median OS was 35 months. No significant differences were observed between R0 and R1 patients (28).

Meta-analysis and main retrospectives series on chemotherapy

In 2010, Horgan *et al.* published a large meta-analysis evaluating 6,712 BTC patients (1,797 pts were treated with adjuvant treatment) enrolled in single randomized trials of CTX alone in two SEER registry analyses and in 17 retrospective institutional series (29). Eligible studies included patients with eCCA, iCCA and gallbladder cancers who underwent curative resection [negative (R0) or microscopically positive (R1) margins] as a control group. Nine of the studies were on RT alone, three on CTX alone, and eight on RT-CTX combinations. Only one study was focused on patients with iCC. Compared with surgery alone, adjuvant treatment produced no statistically significant improvement in five-year survival [pooled odds ratio (OR) 0.74, 95% CI: 0.55–1.01]. Separate analysis of gallbladder and bile duct cancers yielded similar results. Survival benefit was statistically significant when data from the two large registry series (1,233 patients) were excluded (OR 0.53, 95% CI: 0.39–0.72). Concerning gallbladder and bile duct cancers there was a significant survival benefit for CTX (OR 0.39, 95% CI: 0.23–0.66) and chemoradiotherapy (OR 0.61, 95% CI: 0.38–0.99) but not for RT alone (OR 0.98, 95% CI: 0.67–1.43). A statistically significant OS advantage was reported for adjuvant CTX (77% of patients) or chemoradiotherapy in node-positive patients (OR 0.49, 95% CI: 0.30–0.80) analyzing pooled data from nine studies which included at least half of the patients with confirmed nodal or marginal disease. Likewise, patients with margin-positive disease seemed to benefit from adjuvant therapy (OR 0.36, 95% CI: 0.19–0.68). Nearly two-thirds of them (63%) had received RT alone. Conversely the majority of studies with R0-resection patients used chemoradiotherapy and most included node-positive patients. For patients without nodal involvement, data were limited and not sufficient to reach definitive conclusions on the benefits of adjuvant therapies. In conclusion, Horgan *et al.*'s meta-analysis seems to support current practice even if it does not pinpoint the best treatment strategy for high-risk patients (i.e., node-positive or marginal disease) nor does it quantify the benefit of adjuvant therapy for patients with low-risk disease. Furthermore, it has some limitations. Firstly the bibliographic

search was restricted to studies published in English. Secondly, the authors did not assess the heterogeneity of the studies in individual analyses. Lastly, only a few demographic details of the patients included were reported.

A first retrospective series included 263 Thai patients who underwent radical resection for CCA between 2009 and 2011. One hundred and thirty-eight received adjuvant CTX while the remaining 125 underwent observation. Various CTX regimens were included, both single agents (gemcitabine, 5-FU or capecitabine) and combination regimens (such as gemcitabine/capecitabine or 5-FU/mitomycin C). The CTX group included younger patients than the control group. Furthermore patients in the CTX group had a better liver function and/or post-surgery recovery (nutritional status) since their albumin levels were higher. The OS was longer in the CTX group than in the observation cohort (21.6 *vs.* 13.4 months, $P=0.01$). Patients who received adjuvant treatment were 35% less likely to die at any time earlier than those who did not (HR 0.65; 95% CI: 0.47–0.91). High-risk disease features (such as high level of CA 19-9, advanced stage, nodal involvement and marginal resection) seemed to be related to a greater benefit of CTX (30).

The effectiveness of adjuvant CTX with gemcitabine and S-1 was retrospectively evaluated in another Japanese case series. S-1 is an oral anticancer drug combining three compounds, namely tegafur, gimeracil and oteracil potassium. One hundred and three patients with UICC IIA-IIB stage BTC and R0/R1 resection were included: 50 were treated with adjuvant CTX while 53 had observation alone. Five-year OS rates were 57% and 24%, respectively. Statistical significance was reached in both R0 and R1 patient subgroups ($P=0.022$ and $P=0.012$, respectively). Conversely, a survival benefit was only detected in the node-positive patient subgroup ($P=0.006$), but not in the node-negative patients ($P=0.213$) (31).

Meta-analysis on radiotherapy and chemoradiotherapy

Two meta-analyses summarized the available evidence on adjuvant RT: the first focused on eCCA, the second on iCCA. Bonet Beltrán *et al.* included 858 patients enlisted in 13 cohort studies (from 1995 to 2008) (32). Overall, 400 patients were treated with adjuvant RT and 458 with surgery alone. Pooled HR for OS was equal to 0.72 (95% CI 0.53–0.98, $P=0.037$) in favor of the addition of RT. A high statistical heterogeneity (I^2 index =49.3%) was reported due to the imbalanced tumor origin. Focusing on eCCA alone, the pooled HR was 0.62 (95% CI: 0.48–0.78, $P<0.001$) in favor of RT, with low heterogeneity

(I^2 index =4% and a non-significant Cochran's Q test). However, this study presents some limitations. Firstly, all the studies included were retrospective. The number of patients in each cohort was small (on average 58 patients) and the impact of concurrent systemic CTX is unknown due to the lack of individual data. Finally the patients included in the RT groups more often had adverse features (e.g., positive surgical margins and/or metastatic lymph nodes) (32).

Shinohara *et al.* conducted a SEER database pooled analysis between 1988 and 2003 (33). They included 3,839 iCCA patients in four distinct treatment groups: surgery and adjuvant RT (286 pts), surgery alone (948 pts), RT alone (396 pts) and no treatment (2,209 pts). Surgery plus RT was associated with an improvement in median OS compared to surgery alone (11 *vs.* 6 months $P<0.0138$) and a reduced hazard ratio of death (HR 0.78, 95% CI: 0.67–0.92) both at univariate and multivariate analysis. The authors concluded that adjuvant RT could extend survival. The potential limitations of this study are: missing data regarding the type of surgery and N stage; missing data on T stage for near 70% of cases; lack of selection criteria for adjuvant RT; poor depiction of RT modality (e.g., irradiation technique, field covered, total dose delivered, fractions and length of treatment, rate of treatment completion, toxicities). Overall, the authors concluded that adjuvant RT could extend survival even if the evidence provided by their work is poor (33).

Ongoing trials

To date, the only randomized ongoing trial of adjuvant CTX in BTC is the ACTICCA-1 study. This is a large multinational phase III trial (NCT02170090) currently recruiting patients with resected BTC and randomly assigning them to adjuvant CTX with cisplatin and gemcitabine or observation. The primary endpoint is DFS (34).

Predictive factors of response

In order to optimize the clinical benefit of an adjuvant treatment after surgical resection for BTC, potential predictive factors of response need to be identified.

Intracellular uptake of gemcitabine is mediated by a specialized membrane nucleoside transporter, namely human equilibrative nucleoside transporter 1 (hENT-1) (35). Based on the results of retrospective studies in patients with locally advanced or metastatic CCA (35) and pancreatic cancer, treated with gemcitabine-based CTX, our group examined the putative role of hENT-1 as a predictive

factor in patients who received adjuvant gemcitabine after surgical resection for CCA (36). Seventy-one CC tissue samples were retrospectively analyzed for hENT1 tumor cell localization: 23 (32.4%) cases were completely negative for the transporter, 22 (31.0%) showed only cytoplasm positivity, and 26 (36.6%) had concomitant membrane/cytoplasm immunoreactivity. After pooling hENT-1-negative patients and those positive for hENT-1 in only the cytoplasm of tumor cells, survival analysis showed that membrane-positive hENT-1 was associated with a longer DFS (HR 0.49, 95% CI: 0.24–0.99) than membrane-negative hENT-1 (36).

A retrospective study by Kobayashi *et al.* analyzed a series of 105 patients with BTC who underwent curative resection and then received adjuvant CTX with gemcitabine alone or in association with S-1. Fifty-four patients underwent observation alone. In the subgroup of 51 patients treated with adjuvant gemcitabine-based CTX, hENT1 expression was the only independent predictive factor for OS at multivariate analysis (HR 2.77, $P=0.027$) (37). Given the retrospective design of these studies and the different CTX regimens employed, future prospective clinical trials on larger populations are required to confirm the potential interaction between hENT-1 localization and the outcome of CCA patients receiving adjuvant gemcitabine.

Other potential biomarkers for gemcitabine response include the activities of cytidine deaminase (CDA), deoxycytidine kinase, and ribonucleotide reductase M1. Yoon and colleagues examined whether single nucleotide polymorphisms (SNPs) in encoding genes involved in the transport and metabolism of gemcitabine were associated with its efficacy in treating BTC. A retrospective analysis of 80 patients with advanced BTC treated with gemcitabine plus cisplatin found that an SNP in the CDA (cytidine deaminase) gene (*CDA* 435 C>T polymorphism) was significantly associated with tumor response (OR 0.23, 95% CI: 0.06–0.93, $P=0.039$), suggesting a putative role of CDA activity in predicting the efficacy of gemcitabine-based CTX (38).

Unsolved questions

The main open questions are: the timing of treatment, the dose of RT, and effectiveness and safety in the elderly.

Timing of treatment

This is often based on empirical data. Therapy usually starts within two months after surgery and lasts for 6 months. No study has specifically addressed this issue or the optimal

length of therapies. Moreover these parameters vary widely among the studies described above.

Dose of radiotherapy

There is a great heterogeneity among the RT studies. The total RT dose differs (ranging from 40 to 50 Gy) as does the regimen (normal *vs.* split course). Sometimes a combination with boosts (brachytherapy or intra-operative RT) is pre-planned (this translates into different lengths of treatment). The duration of concurrent chemoradiation also differs among the studies and in general depends on the RT protocol.

Elderly patients

Given their retrospective design, the vast majority of studies had no clear cut-off for age. Most patients were treated according to the risk of relapse and performance status. Among the few randomized trials available, the majority allowed inclusion unrestricted by age (22,26,28). The Japanese trial did not enroll patients older than 75 years (23). The two large meta-analyses by Horgan *et al.* and Bonet Beltrán *et al.* do not provide details on the age of patients treated with CTX alone, RT alone or a combination (32). On the basis of the available data, we could only assess the adjuvant treatment for elderly patients as feasible. Further investigations are required to fully understand its effectiveness.

Conclusions

Adjuvant treatments such as CTX, RT or chemoradiotherapy are widely employed in BTC, even if they have mainly been explored in small retrospective series until recently. Available data and meta-analyses suggest that adjuvant strategies, especially CTX, could reduce the risk of relapse and potentially improve OS. Subgroups of high-risk patients such as those with microscopically non-radical resection or with nodal involvement seem to benefit most from adjuvant CTX and/or RT. Some retrospective studies investigated the putative role of hENT1 expression and cytidine deaminase polymorphisms as predictive factors of the effectiveness of gemcitabine-based CTX. To date, 5-FU (and prodrugs) or gemcitabine have been the mainstay of adjuvant strategies for BTC. After the recent results of the BILCAP trial, capecitabine has emerged as a referral drug in this setting. Specific issues on the length and timing of treatment, feasibility in the elderly, RT modalities and the efficacy of combination therapies still need to be solved.

Acknowledgments

Funding: None.

Footnote

Provenance and peer review: The article was commissioned by the editorial office, *Translational Cancer Research* for the series "Primary Liver Cancer". The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2018.08.17>). The series "Primary Liver Cancer" was commissioned by the editorial office without any funding or sponsorship. GB served as the unpaid Guest Editor of the series and serves as the unpaid editorial board members of *Translational Cancer Research* from Jan 2019 to Dec 2020. The authors have no other conflicts of interest to declare.

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Palloni A, Frega G, De Lorenzo S, Rizzo A, Abbati F, Deserti M, Tavolari S, Brandi G. Adjuvant treatment in biliary tract cancer. *Transl Cancer Res* 2019;8(Suppl 3):S289-S296. doi: 10.21037/tcr.2018.08.17