# Adjuvant therapy in biliary tract and gall bladder carcinomas: a review

## Roshan S. Prabhu, Jimmy Hwang

Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

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*Correspondence to:* Roshan S. Prabhu, MD, MS. Levine Cancer Institute, Carolinas HealthCare System, 1021 Morehead Medical Drive, Suite 1000, Charlotte, NC 28204, USA. Email: roshan.prabhu@carolinashealthcare.org.

**Abstract:** Biliary tract carcinomas are relatively rare, but are increasingly diagnosed. They comprise several anatomically contiguous sites, so are often grouped together, but they do appear to represent distinct diseases, in part because of anatomical and surgical considerations. Complete upfront surgical resection is generally difficult because these cancers are often diagnosed at relatively advanced stages of disease. Thus, adjuvant therapy is often considered. This paper will review the evidence underpinning current recommendations for adjuvant therapy in biliary carcinomas.

Keywords: Cholangiocarcinoma gall bladder carcinoma; adjuvant therapy; radiation therapy

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## Introduction

Cancers of the biliary tract are a relatively rare and aggressive disease that generally present at a locally advanced stage. However, certain geographic areas have a higher incidence of these diseases, and they may be increasing in incidence. The cancer is most commonly adenocarcinoma, arising from the epithelium of the gallbladder, intrahepatic, or extrahepatic biliary ducts. Extrahepatic cholangiocarcinoma (EHCC) is sub-classified anatomically as hilar or distal common bile duct (CBD), usually depending on the relation to the cystic duct insertion. The majority of cholangiocarcinoma is hilar (60–70%), followed by distal CBD (20–30%), and intrahepatic (5–15%) (1).

Risk factors for cholangiocarcinoma are generally related to inflammation and include primary sclerosing cholangitis, chronic choledocolithiasis, and liver fluke infections. Risk factors for gallbladder cancer (GBC) are also generally inflammation mediated and include chronic cholelithiasis, gallbladder calcification (porcelain gallbladder), gallbladder polyps, and inflammatory bowel disease (2,3).

Upfront surgical resection is the mainstay of therapy in patients who are anatomically and medically fit for surgery (4). Approximately 65% of patients who undergo surgical exploration with hilar cholangiocarcinoma will have resectable disease. However this rate is less than 50% if resectable is defined as curative surgery with negative margins (R0) (5). Resectability and overall survival (OS) are well stratified by TNM stage at presentation with 5-year OS for AJCC 7<sup>th</sup> edition stage I EHCC of 30%, 24% for stage II–III, and 2% for stage IV (6). Stages for stage outcomes are worse for intrahepatic cholangiocarcinoma (ICC).

A predominant pattern of recurrence in patients with biliary cancers is through hematogenous spread of metastatic disease to liver and lung, and to locoregional and distant lymph nodes (LN). Among the difficulties of determining the optimal therapy for biliary cancers is the relative infrequency and the heterogeneity of these diseases. NCCN guidelines offer several options for GBC or cholangiocarcinoma status post resection. These options include observation, adjuvant chemotherapy, or

adjuvant chemoradiation (CRT) (4). Due to the relatively rare nature of these cancers, level I evidence based on randomized controlled trials is generally not available to guide therapy decisions in the adjuvant setting. Treatment recommendations must be based on lower levels of evidence, most commonly single institution retrospective studies.

The purpose of this review is to summarize the existing published literature for the adjuvant management of GBC and cholangiocarcinoma and examine the relative merits of these data in shaping the current standards of care.

#### GBC

GBC is the most common type of biliary tract cancer. Outcomes depend highly on stage with 5-year OS of 60%, 39%, and 15%, 5%, and 1% for stages 0, I, II, III, and IV, respectively (7). The standard of care is initial resection with cholecystectomy, en bloc hepatic resection, and lymphadenectomy with the goal of R0 resection. Patients with pT1N0 tumors are recommended to be observed. Options for adjuvant therapy post resection of pT2 or above or LN positive disease include fluoropyrimidine based CRT, fluoropyrimidine or gencitabine based chemotherapy, or observation (4) (*Table 1*).

There is evidence that the patterns of failure for resected GBC may be distinct from that of EHCC. A single institution retrospective study of 177 patients, of whom 97 (55%) had GBC and 80 (45%) had hilar cholangiocarcinoma, reported patterns of first recurrence (13). The minority of patients (11%) received any adjuvant therapy. Overall recurrence was higher and time to first recurrence was shorter for GBC compared with hilar cholangiocarcinoma. Of patients with recurrence, isolated locoregional recurrence (LRR) as 1<sup>st</sup> recurrence occurred in 15% of patients with GBC compared with 59% of those with hilar cholangiocarcinoma (P<0.001). Distant recurrence (with or without LRR) occurred in 85% of patients with GBC compared with 41% of those with hilar cholangiocarcinoma (P<0.001). Primary site was an independent predictor of site of initial recurrence controlling for other clinico-pathologic factors.

## Adjuvant chemotherapy

The strongest data in support of adjuvant systemic therapy for any of the biliary tract carcinomas is derived from a Japanese study reported by Takada *et al.*, and more specifically applies to gall bladder adenocarcinomas (14). In this study, a heterogenous group of 508 patients with pancreatic, ampullary, biliary, and gall bladder cancers, underwent resection between 1986 and 1992. One hundred and forty patients with gall bladder cancers were enrolled. Patients were randomly assigned to undergo observation, or to receive adjuvant therapy with Mitomycin C 6  $mg/m^2$  on the day of surgery, then 5-fluorouracil (5-FU) 310 mg/m<sup>2</sup> IV daily for 5 days on week 1 and 3 postoperatively, then oral 5-FU 100 mg/m<sup>2</sup> daily starting in week 5. Overall, the study failed to demonstrate a survival benefit at 5 years, the primary endpoint, and the only patients that did demonstrate a significant survival benefit were those with gall bladder cancer. The 5-year OS of patients with gall bladder cancer receiving adjuvant therapy was 26.0%, compared to 14.4% in those who were observed.

In addition, a meta-analysis that focused specifically on gall bladder cancers demonstrated that adjuvant chemotherapy did improve survival compared to surgery alone (15). However, an evaluation of the National Cancer Database (NCDB) did not demonstrate a survival benefit with adjuvant chemotherapy (16).

# Adjuvant RT/CRT

Due to the relatively small number of GBC cases, the current standards of care are based primarily on population based analyses utilizing Surveillance, Epidemiology, and End Results (SEER) data.

An initial study using the SEER database for patients with GBC diagnosed between 1992 and 2002 was reported in 2007 (8). SEER does not contain chemotherapy information; hence this was a study of adjuvant RT (concurrent chemotherapy use unknown) versus no adjuvant RT. A total of 3,187 cases were identified, of which 17% received adjuvant RT. Median OS was 14 months compared with 8 months (P<0.001) for those who did and did not receive RT, respectively. Subset analysis according to disease extent found the OS benefit with RT was limited to those with regional spread (LN positive disease) or liver involvement (pT3 according to AJCC 7<sup>th</sup> editions staging).

A SEER study with a largely overlapping patient population (incident cases from 1988–2003) was published in 2008 (9). This study generated nomograms for prediction of short term OS with and without adjuvant RT. On multivariate analysis, age, gender, papillary histology, stage, and adjuvant RT were significant predictors of OS. The model predicted a significant OS benefit with adjuvant RT

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Author and Year	Description of study	Results	Conclusions
Mojica e <i>t al.</i> [2007] (8)	SEER database 1992–2002; resected GBC; adjuvant RT vs. no adjuvant RT	3,187 cases; 17% received adjuvant RT; median OS (adjuvant RT vs. no adjuvant RT): 14 vs. 8 months (P<0.001); OS benefit limited to pT3-T4 or pN+ disease	Adjuvant RT associated with improved OS for patients with resected GBC; most benefit seen for those with pT3-T4 or pN+ disease
Wang <i>et al.</i> [2008] (9)	SEER database 1998–2003; resected GBC; adjuvant RT vs. no adjuvant RT; nomogram developed for prediction of benefit based on clinico-pathologic factors	4,180 cases; 18% received adjuvant RT; on multivariate analysis, age, gender, papillary histology, stage, and adjuvant RT were significant predictors of OS	The model predicted a significant OS benefit of varying degree with adjuvant RT for patients with ≥ pT2 or pN+ disease
Wang <i>et al.</i> [2011] (10)	SEER-Medicare linked database 1995– 2005; resected GBC	1,137 cases; 11% received adjuvant chemotherapy; 11% received adjuvant CRT	Adjuvant CRT was found to provide a modest, but significant, OS benefit for patients with pT2–T3N0 disease, with the largest benefit for patients with pT4 or pN+ disease; adjuvant chemotherapy alone did provide a small benefit for patients with pT4 or pN+ disease, but this was significantly smaller than the benefit from adjuvant CRT
Ben-Josef <i>et al.</i> [2015] (11)	SWOG S0809; multi-institutional single arm phase II trial; included resected GBC or EHCC (pT2-T4 or pN+ or R1 resection); 4 cycles of adjuvant Gem/Cape followed by concurrent Cape/RT to 54–59.4 Gy	79 eligible patients; 25 (32%) had GCB; 86% treatment compliance rate; 2-year results for GCB subset: OS: 56%, DFS: 47%, LR: 8%	Promising regimen found to be effective and tolerable compared with historical controls
Horgan <i>et al.</i> [2012] (12)	Meta-analysis of published studies (primarily retrospective) of adjuvant therapy that included a comparator arm without adjuvant therapy adjuvant therapy	6 studies of resected GBC were included: 4 single institution studies, 1 prospective randomized trial of adjuvant chemotherapy, 1 SEER analysis (9); 3 studies of adjuvant CRT: 2 of adjuvant RT, 1 of adjuvant CRT: 2 of adjuvant RT, 1 of adjuvant chemotherapy; the GCB pooled analysis did not show an overall OS benefit with adjuvant therapy (P=0.41)	The GCB pooled analysis did not show an overall OS benefit with adjuvant therapy (P=0.41); however, the combined analysis with resected cholangiocarcinoma did demonstrate a strong trend towards benefit with adjuvant therapy (OR 0.74, P=0.06); adjuvant therapy (OR 0.61, P=0.49) provided significantly more benefit in OS than adjuvant RT alone (OR 0.98, P=0.9); any adjuvant therapy (including RT alone) had a significant benefit in patients with R1 resection (OR 0.36, P=0.002) or pN+ disease (OR 0.49, P=0.004)
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for patients with  $\ge pT2N+$  (LN positive) disease. Patients with pT1 disease did not benefit regardless of LN status and those with  $\ge pT2N0$  disease had variable benefit that was dependent on other model variables.

A follow-up study published in 2011 by the same group used SEER-Medicare linked data, which contained information on both RT and chemotherapy use (10). A total of 1,137 patients with GBC resected between 1995 and 2005 were included. A minority of patients received either adjuvant chemotherapy (11%) or CRT (11%). The primary end point was OS with or without adjuvant chemotherapy or CRT. Adjuvant CRT was found to provide a modest, but significant, OS benefit for patients with pT2-T3N0 disease, with the largest benefit for patients with pT4 or pN+ disease. Adjuvant chemotherapy alone did provide a small benefit for patients with pT4 or pN+ disease, but this was significantly smaller than the benefit from adjuvant CRT. These results were partially mirrored in a retrospective Korean study of 100 patients with resected GCB (17). They found a significant benefit in disease free survival (DFS) and disease specific survival (DSS) for adjuvant CRT for patients with pT2-T3N+, but no benefit for pT2-T3N0.

A recently published prospective multi-institutional phase II trial (SWOG S0809) included patients with resected GBC or EHCC, pT2-T4 or pN+ or R1 resection status (11). Treatment consisted of 4 cycles of gemcitabine and capecitabine followed by concurrent capecitabine with RT to a total dose of 54–59.4 Gy. There were 79 eligible patients, of which 25 (32%) had GCB. Treatment compliance was high with 86% of patients completing therapy. The 2-year OS, DFS, and local recurrence (LR) rates were 56%, 47%, and 8% for GBC subset, respectively. These outcomes did not differ significantly from the EHCC subset. This regimen was found to be effective, tolerable, and a promising adjuvant regimen compared with historical controls.

A meta-analysis of primarily retrospective studies of adjuvant therapy that included a comparator arm without adjuvant therapy was published in 2012 (12). Six studies of patients with resected GBC were included, of which four were single institution retrospective studies and 1 was a randomized trial of adjuvant chemotherapy alone, all of which consisted of a total of 270 patients. The 6<sup>th</sup> study was the aforementioned SEER study by Wang *et al.* of 4,180 patients (9). Three studies were of adjuvant CRT, 2 reported on adjuvant RT alone, and 1 was of adjuvant chemotherapy. The GCB pooled analysis did not show an overall OS benefit with adjuvant therapy (P=0.41). However, the combined analysis with resected cholangiocarcinoma did demonstrate a strong trend towards benefit with adjuvant therapy [odds ratio (OR) 0.74, P=0.06]. When separated by treatment modality, adjuvant chemotherapy (OR 0.39, P<0.001) and adjuvant CRT (OR 0.61, P=0.49) provided significantly more benefit in OS than adjuvant RT alone (OR 0.98, P=0.9, significant treatment interaction by modality, P=0.02). Any adjuvant therapy (including RT alone) had a significant benefit in patients with R1 resection (OR 0.36, P=0.002) or pN+ disease (OR 0.49, P=0.004).

In the context of the other aforementioned studies, these data support the use of adjuvant therapy (chemotherapy or CRT) for patients with  $\ge$  pT2, pN+, or R1 resected GBC, with the most benefit in those with R1 resection or pN+ disease.

## **Biliary tract carcinoma**

## Adjuvant chemotherapy

Most studies evaluating the potential benefits of adjuvant chemotherapy in biliary tract carcinomas included all anatomic sites, limiting the power of the conclusions that can be drawn. For example, the trial reported by Takada *et al.* included pancreatic, ampullary and biliary carcinomas as well as gall bladder carcinomas (14). While there was a suggestion of benefit in the group of patients with gall bladder carcinomas, the study did not demonstrate a survival benefit overall. Since ESPAC-1 and CONKO-001 both demonstrated a survival benefit for adjuvant chemotherapy with 5-FU/Leucovorin and Gemcitabine, respectively, in pancreatic adenocarcinomas, these results suggest that this type of regimen may be ineffective in biliary and ampullary carcinomas (18,19).

A lack of benefit of adjuvant chemotherapy is reinforced by a subgroup of 428 patients from the ESPAC-3 study with carcinoma of the bile duct, ampulla and periampullary duodenum (20). Most had ampullary carcinomas, and only 96 had biliary carcinomas. Patients were randomly assigned to observation, 5-FU/Leucovorin on a Mayo Clinic schedule (bolus 5-FU and leucovorin for five consecutive days, with cycles repeated every four weeks), or gemcitabine. Since the ESPAC-3 overall analysis did not demonstrate a difference in survival outcomes between the two chemotherapy regimens, the chemotherapy groups were assessed together. While the survival was longer in patients who were treated with chemotherapy (median 43.1 months, compared to 35.2 months with observation), the difference was not statistically significant [hazard ratio (HR) 0.86, P=0.25].

Because of the limited category A level evidence to help guide management recommendations and decisions in biliary tract cancer, Horgan *et al.* performed a metaanalysis on studies that were published through 2010 (12). The published reports including retrospective studies on patients, and included a total of 6,712 patients, that comprised 4,915 patients who underwent surgery alone, and 1,297 who had received chemotherapy, and/or radiation. The investigators reported that overall, there was no survival benefit with adjuvant therapy. This was especially true for patients who were treated with radiation alone (OR 0.98), but patients who received chemotherapy with (OR 0.61, P=0.049) and without radiation (OR 0.39, P<0.0001) did have improved survival compared to surgery alone.

# EHCC

EHCC are adenocarcinomas that arise from the biliary tree, outside of the liver parenchyma. They are further subdivided into hilar and distal CBD cholangiocarcinomas based on their location relative to the cystic duct insertion. EHCC are significantly more common than intrahepatic, though both are relatively rare compared with other cancers of the GI tract.

Expected outcomes for EHCC also depend highly on stage and resectability, with 5-year OS of 30%, 24%, and 2% for local disease (stage I), regional spread (stages II–III), and distant spread (stage IV), respectively (http://www.cancer. org/cancer/bileductcancer/detailedguide/bile-duct-cancer-survival-by-stage). Hilar cholangiocarcinoma can be staged according to AJCC 7<sup>th</sup> edition (6) or more specialized local staging systems, including modified Bismuth *et al.* (21) and Blumgart staging systems (22).

Margin negative surgical resection is the mainstay of initial therapy for resectable patients. The typical surgery for hilar cholangiocarcinoma is extended hepatectomy while pancreaticoduodenectomy (PD) is utilized for distal EHCC (23). Negative margins are a major prognostic factor, with some evidence that widely negative margins ( $\geq 1$  cm) confer even more benefit in terms of long term survival (24). As opposed to GCB, the primary pattern of failure for resected EHCC is loco-regional (13).

In the setting of R0 resection and negative LN, NCCN guidelines recommend observation, fluoropyrimidine based CRT, or fluoropyrimidine or gemcitabine based chemotherapy at the same level 2A recommendation (4). In

the setting of incomplete resection (R1 or R2) or positive LN, the recommendations are fluoropyrimidine based CRT followed by fluoropyrimidine or gemcitabine based chemotherapy or fluoropyrimidine or gemcitabine based chemotherapy alone if R0 and pN+.

# Adjuvant RT/CRT

No randomized trials have been performed investigating the role or optimal regimen for adjuvant therapy for resected EHCC. There have been many small single institutional retrospective studies over several decades that shape our current understanding. We will focus on the selected studies that form the basis of the current standards of care for adjuvant therapy in resected EHCC (*Table 2*).

Several retrospective studies have investigated the use of surgery with adjuvant CRT compared with a historical cohort of surgery alone. A study from Johns Hopkins University included 34 cases of adenocarcinoma of the distal CBD treated with PD with adjuvant CRT (25). The 5-year OS was 35%, with LN status being the most important prognostic factor (5-year OS 100% for pN0 vs. 24% for pN+). Five-year local control was 70%, with all patient deaths due to progressive metastatic disease. Median OS was significantly longer in this cohort treated with PD and adjuvant CRT compared with the historical control of 30 patients treated with PD alone (36.9 vs. 22 months, P<0.04). A retrospective study from Korea included patients with resected EHCC treated with or without adjuvant CRT in the same 2001-2009 time period (26). Of the 168 patients, 115 received adjuvant CRT (68%) and 53 (32%) did not. Five-year LRC, DFS, and OS rates were significantly improved with adjuvant CRT (58.5% vs. 44.4%, P=0.007; 32.1% vs. 26.1%, P=0.041; 36.5% vs. 28.2%, P=0.049, respectively). Adjuvant CRT remained a significant independent prognostic factor for LRC, DFS, and OS on multivariable analysis (P<0.05). A similar, but larger analysis of 336 Korean patients was published in 2015 (27). Patients with resected EHCC were treated with surgery alone (50%), adjuvant chemotherapy (27%), adjuvant RT (9%), or adjuvant CRT (15%). Both surgery with adjuvant chemotherapy or CRT groups demonstrated significantly improved OS compared with surgery alone (P<0.05), with surgery + RT having borderline significance (P=0.078). In the subset of patients with R1 resection, surgery followed by CRT significantly improved OS (P<0.05).

Several population based studies have been published to help inform this clinical question. Two studies published

Author and year	Description of study	Results	Conclusions
Hughes <i>et al.</i> [2007] (25)	Single institution retrospective study; resected EHCC; adjuvant CRT vs. surgery alone	34 patients treated with adjuvant CRT compared with 30 patients treated with surgery alone; median OS: 36.9 months vs. 22 months, P<0.04; adjuvant CRT cohort outcomes: 5-year OS 35%, 5-year LRC; 70%; pN status most important prognostic factor; 5-year OS 100% for pN0 vs. 24% for pN+	Adjuvant CRT associated with significant OS benefit compared with surgery alone for resected EHCC
Kim e <i>t al.</i> [2011] (26)	Korean retrospective study; resected EHCC 2001–2009; adjuvant CRT vs. surgery alone	168 patients: 115 (68%) adjuvant CRT, 53 (32%) surgery alone; 5-year LRC, DFS, and OS rates were significantly improved with adjuvant CRT: LRC: 58.5% vs. 44.4%, P=0.007, DFS: 32.1% vs. 26.1%, P=0.041, OS: 36.5% vs. 28.2%, P=0.049	Adjuvant CRT associated with significant benefit for LRC, DFS, and OS compared with surgery alone for resected EHCC
Im <i>et al.</i> [2015] (27)	Korean retrospective study; resected EHCC; adjuvant CRT, chemotherapy, or RT vs. surgery alone vs. surgery alone	336 patients; 50% surgery alone, 27% adjuvant chemotherapy, 9% adjuvant RT, 15% adjuvant CRT; both adjuvant chemotherapy and CRT groups demonstrated significantly improved OS compared with surgery alone (P<0.05), with surgery + RT having borderline significance (P=0.078); in the subset of patients with R1 resection, only adjuvant CRT significantly improved OS (P<0.05)	Adjuvant chemotherapy or CRT significantly improved OS compared to surgery alone for resected EHCC; adjuvant CRT is most effective for R1 resection
Hoehn <i>et al.</i> [2015] (16)	NCDB database analysis Resected EHCC; adjuvant chemotherapy or CRT versus surgery alone	8, 134 patients; 71% surgery alone, 6% adjuvant chemotherapy, 24% adjuvant CRT; multivariate analysis demonstrated significantly improved OS with adjuvant CRT (HR 0.82; 95% Cl, 0.75–0.91), regardless of margin status (R0: HR 0.88; 95% Cl, 0.79–0.97; R1: HR 0.49; 95% Cl, 0.38–0.62); adjuvant chemotherapy not significant	Adjuvant CRT was associated with a significant improvement in OS compared to surgery alone for resected EHCC; adjuvant chemotherapy was not associated with an OS benefit
Borghero <i>et al.</i> [2008] (28)	Single institution retrospective study; resected EHCC; Comparison of high risk patients (R1 or pN+) treated with adjuvant CRT vs. Iow risk patients (R0pN0) treated with surgery alone	42 "high risk" patients; 23 "low risk" patients; no difference in 5-year OS (36% vs. 42%, P=0.6) or 5-year LRR (38% vs. 37%, P=0.13)	No difference between high risk patients treated with adjuvant CRT and low risk patients treated with surgery alone indicates the ability of adjuvant CRT to mitigate the effects of high risk factors (R1 or pN+) in resected EHCC
Table 2 (continued)			

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Table 2 (continued)			
Author and year	Description of study	Results	Conclusions
Park <i>et al.</i> [2011] (29)	Single institution retrospective study; resected EHCC; all patients received adjuvant CRT; comparison of R0 vs. R1 patient cohorts	51% R0 resection, 49% R1 resection; no difference in 5-year OS (44% vs. 33%, P=0.28), PFS (35% vs. 22%, P=0.31), or locoregional PFS (75% vs. 63%, P=0.28) rates for R0 vs. R1 groups	No difference in outcomes for R1 vs. R0 patients treated with adjuvant CRT indicates the ability of adjuvant CRT to mitigate the effects of R1 resection
McNamara <i>et al.</i> [2015] (30)	Retrospective study; resected EHCC; goal to determine benefit of adjuvant chemotherapy or CRT based on resection status and pN status	296 patients; any adjuvant therapy was associated with an OS benefit for patients with R1 resection (HR 0.23, P<0.05), but not for patients with R0 resection (HR 0.91, P>0.05); the same was true for patients with pN+ disease (HR 0.46, P<0.05) compared with pN0 disease (HR 0.73, P>0.05)	Benefit of adjuvant therapy (chemotherapy or CRT) was limited to higher risk patients—those with R1 resection or pN+
Kim <i>et al.</i> [2016] (31)	Korean retrospective study; resected EHCC; all patients had R0 resection; goal was to determine benefit of adjuvant chemotherapy or CRT based on pN status	158 patients; multivariable analysis demonstrated significant improvement in OS after chemotherapy (HR 0.21; 95% Cl, 0.08– 0.53; P=0.001) and CRT (HR 0.25; 95% Cl, 0.08–0.83; P=0.024); this benefit was significant in the R0 setting regardless of pN status	Patients has significant benefit with adjuvant chemotherapy or CRT in the R0 resection setting regardless of pN status
Lim <i>et al.</i> [2009] (32)	Korean retrospective study; resected EHCC; all patients treated with adjuvant CRT; goal was to determine benefit of adjuvant chemotherapy in addition to adjuvant CRT	120 patients: 90 adjuvant CRT alone, 30 adjuvant CRT and chemotherapy; CRT with adjuvant chemotherapy demonstrated significantly improved DFS (45.2% vs. 26.6%, P=0.04) and OS (62.6% vs. 30.8%, P<0.01) compared with adjuvant CRT alone	The addition of adjuvant chemotherapy to adjuvant CRT was associated with a significant benefit in DFS and OS for resected EHCC
Ben-Josef <i>et al.</i> [2015] (11)	SWOG S0809; multi-institutional single arm phase II trial; included resected GBC or EHCC (pT2-T4 or pN+ or R1 resection); 4 cycles of adjuvant Gem/Cape followed by concurrent Cape/RT to 54–59.4 Gy	79 eligible patients; 54 (68%) had EHCC; 86% treatment compliance rate; 2-year results for EHCC subset: OS: 68%, DFS: 54%, LR: 13%	Promising regimen found to be effective and tolerable compared with historical controls
Table 2 (continued)			

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Author and year	Description of study	Results	Conclusions
Horgan <i>et al.</i> [2012] (12)	Meta-analysis of published studies (primarily retrospective) of adjuvant therapy that included a comparator arm without adjuvant therapy adjuvant therapy	15 studies of resected EHCC were included: 13 single institution studies, 1 prospective randomized trial of adjuvant chemotherapy, 1 SEER analysis (Vern-Gross 2011); 6 studies of adjuvant CRT, 7 of adjuvant RT, 2 of adjuvant chemotherapy; the EHCC pooled analysis did not show an overall OS benefit with adjuvant therapy (P=0.1)	The EHCC pooled analysis did not show an overall OS benefit with adjuvant therapy (P=0.1); however, the combined analysis with resected GCB did demonstrate a strong trend towards benefit with adjuvant therapy (OR 0.74, P=0.06); adjuvant chemotherapy (OR 0.61, P=0.49) provided adjuvant CRT (OR 0.61, P=0.49) provided significantly more benefit in OS than adjuvant therapy (including RT alone) had a significant benefit in patients with R1 resection (OR 0.36, P=0.002) or pN+ disease (OR 0.49, P=0.004)
EHCC, extrahepatic cholan	giocarcinoma; RT, radiotherapy; CRT, chemoradi	iation; HR, hazard ratio; CI, confidence interval; OR	l, odds ratio.

outcomes using the same SEER dataset. The first was published in 2009 and included 1,569 cases diagnosed between 1973 and 2005 (33). Patients treated with surgery and adjuvant RT had improved median OS compared with those receiving either surgery or RT alone (median OS 26, 25, and 12 months, respectively, P<0.001), and all treatment groups had superior OS compared to patients who received no therapy (median OS 9 months). A second study utilizing the same SEER dataset was published in 2011 (34). A total of 1,491 patients diagnosed between 1973 and 2003 were included. Patients with localized disease had significantly improved OS compared to those with regional disease, with median OS of 33 and 18 months, respectively (P<0.001). However, in contrast to the prior SEER study, the addition of adjuvant RT was not associated with benefit in OS or CSS. Importantly, information on margin status and chemotherapy use is not available in the SEER database. A recent study using the NCDB of 8,134 patients treated between 1998 and 2006 was published in 2015 (16). This study compared surgery alone (71%), adjuvant chemotherapy (6%), and adjuvant CRT groups (24%). Information on margin status, demographic data, chemotherapy use, and treatment center type was available. Multivariate analysis demonstrated significantly improved OS with adjuvant CRT (HR 0.82; 95% confidence interval (CI), 0.75–0.91], regardless of margin status (R0: HR 0.88; 95% CI, 0.79–0.97; R1: HR 0.49; 95% CI, 0.38–0.62).

Several retrospective studies have investigated the ability of adjuvant CRT to mitigate the effects of negative prognostic factors in high risk patients with resected EHCC. A single institutional retrospective study from MD Anderson compared patients with R1 or pN+ disease treated with adjuvant CRT (n=42) to those with R0pN0 disease treated with surgery alone (n=23) (28). Patients in the CRT and surgery alone groups had similar 5-year OS (36% vs. 42%, P=0.6) and LRR (38% vs. 37%, P=0.13), indicating the potential ability of adjuvant CRT to mitigate the negative effects of R1 and/or pN+ disease. A study from Korea included 101 patients with resected EHCC who all received adjuvant CRT, with 51% having an R0 resection and 49% having an R1 resection (29). There was no difference in 5-year OS (44% vs. 33%, P=0.28), PFS (35% vs. 22%, P=0.31), or locoregional PFS (75% vs. 63%, P=0.28) rates for R0 vs. R1 groups.

There is conflicting evidence as to if there are patient subgroups who specifically do or do not benefit from adjuvant therapy based on certain risk factors. A retrospective study of 296 patients compared the benefit of adjuvant chemotherapy or CRT for patients based on margin status and LN status (30). Any adjuvant therapy was associated with an OS benefit for patients with R1 resection (HR 0.23, P<0.05), but not for patients with R0 resection (HR 0.91, P>0.05). The same was true for patients with pN+ disease (HR 0.46, P<0.05) compared with pN0 disease (HR 0.73, P>0.05). A Korean retrospective study of 158 patients' status post R0 resection of EHCC also examined the role of adjuvant therapy (31). Converse to the previous study, multivariable analysis demonstrated significant improvement in OS after chemotherapy (HR 0.21; 95% CI, 0.08–0.53; P=0.001) and CRT (HR 0.25; 95% CI, 0.08–0.83; P=0.024). This benefit was significant in the R0 setting regardless of pN status.

Several studies have investigated the use of both adjuvant CRT and chemotherapy. A retrospective study from Korea included 120 patients with resected EHCC who received adjuvant CRT with (n=90) or without (n=30) additional adjuvant chemotherapy (32). CRT with adjuvant chemotherapy demonstrated significantly improved DFS (45.2% vs. 26.6%, P=0.04) and OS (62.6% vs. 30.8%, P<0.01) compared with adjuvant CRT alone. A recently published prospective multi-institutional phase II trial (SWOG S0809) included patients with resected GBC or EHCC, pT2-T4 or pN+ or R1 resection status (11). Treatment consisted of four cycles of gemcitabine and capecitabine followed by concurrent capecitabine with RT to a total dose of 54-59.4 Gy. There were 79 eligible patients, of which 54 (68%) had EHCC. Treatment compliance was high with 86% of patients completing therapy. The 2-year OS, DFS, and LR rates were 68%, 54%, and 13% for the EHCC subset, respectively. These outcomes did not differ significantly from the GBC subset. This regimen was found to be effective, tolerable, and a promising adjuvant regimen compared with historical controls.

A meta-analysis of primarily retrospective studies of adjuvant therapy that included a comparator arm without adjuvant therapy was published in 2012 (12). Fifteen studies of patients with resected bile duct cancer were included, of which 13 were single institution retrospective studies and 1 was a randomized trial of adjuvant chemotherapy alone, all of which consisted of a total of 771 patients. The 15<sup>th</sup> study was the aforementioned SEER study by Vern-Gross *et al.* of 1,491 patients (34). Six studies were of adjuvant CRT, seven reported on RT alone, and two were of adjuvant chemotherapy. The biliary duct cancer pooled analysis did not show an overall OS benefit with adjuvant therapy (P=0.1). However, the combined analysis with resected GCB did demonstrate a strong trend towards benefit with adjuvant therapy (OR 0.74, P=0.06). When separated by treatment modality, adjuvant chemotherapy (OR 0.39, P<0.001) and adjuvant CRT (OR 0.61, P=0.49) provided significantly more benefit in OS than adjuvant RT alone (OR 0.98, P=0.9, significant treatment interaction by modality, P=0.02). Any adjuvant therapy (including RT alone) had a significant benefit in patients with R1 resection (OR 0.36, P=0.002) or pN+ disease (OR 0.49, P=0.004).

In the context of the other aforementioned studies, these data support the use of adjuvant therapy (chemotherapy or CRT) for patients with resected EHCC, with the combination of CRT and chemotherapy indicated for high risk patients, such as those with R1 resection and/or pN+ status.

# ICC

ICC represents the minority of cholangiocarcinoma, making up only 5–15% of cases (1). Survival outcomes are worse for ICC stage for stage compared with EHCC, with median OS not reached for stage I, 53 months for stage II, and 16 months for stage III (6).

Surgery is the mainstay of therapy and generally consists of hepatic resection with portal lymphadenectomy, but only approximately 30% of patients present with operable disease (35). NCCN guidelines recommend observation or fluoropyrimide or gemcitabine based chemotherapy after R0 resection (4). Options after R1 resection are fluoropyrimidine CRT or fluoropyrimide or gemcitabine based chemotherapy. R2 resection portends a poor prognosis and gemcitabine/cisplatin combination chemotherapy is a category 1 recommendation, with locoregional therapy listed as a category 2B recommendation.

# Adjuvant chemotherapy

While there have not been any prospective or randomized studies evaluating adjuvant chemotherapy in ICC, a number of retrospective single institution studies have suggested that adjuvant chemotherapy is beneficial in this disease (30,36-38). An analysis of the NCDB also supported the potential benefit of adjuvant chemotherapy (39). Several studies have suggested that patients who have a lower likelihood excreting or clearing gemcitabine, as manifested by RRM1 or hENT1 expression are particularly likely

to benefit from adjuvant therapy, possibly representing a useful biomarker (40-42). Nonetheless, taken together, available data provides only modest support for adjuvant chemotherapy for IHCC.

# Adjuvant RT/CRT

Even more so than the other biliary tract cancer sites, there is a lack of prospective or randomized evidence to guide recommendations for IHCC. The largest study is a population based investigation using the SEER database (43). A total of 3839 patients with IHCC were included, of which 25% received surgery alone, 10% received RT alone, 7% surgery and adjuvant RT, and 58% no surgery or RT. Surgery and adjuvant RT provided the most benefit for OS (HR 0.40; 95% CI, 0.34–0.47), followed by surgery alone (HR 0.49; 95% CI, 0.44–0.54) and RT alone (HR 0.68; 95% CI, 0.59–0.77), compared with no surgery or RT.

Only 1 of 20 studies included the meta-analysis of adjuvant therapy in resected biliary tract cancer included patients with ICC (12). Of the 92 patients in this study, only 11 had ICC.

Adjuvant chemotherapy and/or RT demonstrated a trend towards improved OS compared with surgery alone in the entire patient population (Median OS 42 vs. 29 months, P=0.07). However, patients with distal EHCC were the subgroup that received the most benefit with adjuvant therapy.

## Conclusions

While the past several decades have seen advances in the treatment of many cancers, progress in biliary carcinomas has been slow. This is in part because of the heterogeneity of these diseases, making the development and interpretation of clinical trials difficult. This is especially true in the perioperative therapy of biliary cancers, where for the most part, treatment recommendations are based on retrospective series and expert opinion. Nonetheless, there appears to be some consensus that adjuvant therapy may be warranted in patients with incompletely resected disease, either R1 or R2, and potentially in patients with more advanced disease, particularly nodal involvement. Gemcitabine and fluoropyrimidine-based chemotherapy with or without platinum, and with or without radiation are supported, though none is clearly favored as a therapeutic approach. Certainly more studies with future attention to molecular or biomarker approaches in these diseases are necessary to

further advance management recommendations.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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