Defining the Role of Adjuvant Therapy: Cholangiocarcinoma and Gall Bladder Cancer

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Biliary tract cancers are a rare subgroup of malignancies that include gall bladder carcinoma and cholangiocarcinoma. They generally carry a poor prognosis based on the advanced nature of disease at presentation and overall treatment refractoriness. Surgical resection remains the optimal treatment for long-term survival, with consideration of neoadjuvant or adjuvant therapies. In this review, we summarize the role of adjuvant treatments including radiation therapy, chemotherapy, and concurrent chemoradiation with the existing clinical evidence for each treatment decision. Given the rarity of these tumors, the evidence provided is based largely on retrospective studies, Surveillance, Epidemiological, and End Results (SEER) database inquiries, single- or multi-institutional prospective studies, and a meta-analysis of adjuvant therapy studies. Currently, there is no adjuvant therapy that has been agreed upon as a standard of care. Results from prospective, multi-institutional phase II and III trials are awaited, along with advances in molecular targeted therapies and radiation techniques, which will better define treatment standards and improve outcomes in this group of diseases.

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Overview of Biliary Tract Cancer

Biliary tract cancer (BTC) remains a rare oncologic entity that includes gall bladder carcinoma and cholangiocarcinoma. The oncologic biliary tract includes tumors deriving from the epithelium in the gall bladder, as well as intrahepatic and extrahepatic biliary epithelium. In 2012, there were 9810 cases of gall bladder and extrahepatic biliary tumors in the United States, with 3200 deaths. The 5-year overall survival (OS) rate is estimated at 5%-30%. Biliary tract tumors have a higher incidence in Asia, particularly Thailand, Korea, India, and Japan. Most cases are diagnosed with locally advanced disease, distant metastatic disease, or with a combination of both. Prognostic factors include tumor stage, location, nodal involvement, and extent of resection. For metastatic disease, cytotoxic chemotherapy remains the standard of care. There is level I evidence for the use of combination chemotherapy of gemcitabine and cisplatin as first-line therapy for patients with metastatic, locally advanced, or unresectable BTC, based on the results of the ABC-02 trial. In this phase III trial that included patients with cholangiocarcinoma and gall bladder cancer, the addition of cisplatin to gemcitabine-based chemotherapy improved both overall and progression-free survival compared with gemcitabine alone, with a favorable toxicity profile.

In the resectable setting, surgery is typically performed first with consideration of adjuvant therapy including chemotherapy (CT), chemoradiation (CRT), or both based on pathologic findings. Given the rarity of BTC, level I evidence to drive treatment recommendations in the adjuvant setting is limited, with much of the data derived from single-institution phase II trials or, more commonly, retrospective, hypothesis-generating data sets. The situation is further compounded by the inclusion of gall bladder carcinoma, intrahepatic cholangiocarcinoma (IHCC), and extrahepatic cholangiocarcinoma (EHCC) into these studies, which could potentially confound definitive interpretation of results based on anatomical and disease heterogeneity. Consequently, it is difficult to make evidence-based recommendations regarding the use of adjuvant therapy.

Two prospective trials will shed more light on this area. BILCAP is a multi-institution, phase III, randomized clinical trial evaluating adjuvant chemotherapy with capecitabine, a
flourouracil, compared with expectant treatment alone following curative intent resection (R0 or R1) for BTCs. The primary end point is 2-year OS, and the secondary end points include relapse-free survival, toxicity, and quality of life. This trial will provide definitive evidence of the role of adjuvant capecitabine in BTC. SWOG S0809 is a single-arm, prospective, phase II trial of adjuvant capecitabine-gemcitabine chemotherapy followed by concurrent capecitabine and radiotherapy in EHCC, including gall bladder cancer, that completed accrual in 2012. The eligibility criteria included pT2-T4, pN1 disease, or positive margins with no evidence of distant metastases. The primary end point is stratum-specific (R0 or R1) and 2-year OS. Secondary end points include toxicity, stratum-specific disease-free survival (DFS) local failure, and overall DFS. The results of this trial are expected to provide prospective evidence of the role of adjuvant chemotherapy and CRT. In this review, we summarize the existing data regarding the role of adjuvant therapy for gall bladder cancer and cholangiocarcinoma.

Gall Bladder Cancer

Primary malignancy of the gall bladder is rare with an incidence of 4700-5000 cases per year in the United States, making it the most common biliary tract tumor. It is more commonly found in whites as compared with blacks. Risk factors include porcelain gall bladder (calcification) and other conditions that increase local chronic inflammation, such as cholelithiasis. The most common histology of these tumors is adenocarcinoma, with rare cases of small cell carcinoma, squamous cell carcinoma, and sarcoma. Of all the BTCs, gall bladder cancer is arguably the most aggressive type and is associated with the worst prognosis, with a death rate of 2800 per year in the United States. This is, in part, due to the difficulty in detecting this disease early, with symptoms that overlap with benign diagnoses (eg, biliary colic), leading to advanced disease at presentation. In many cases, gall bladder cancer is detected incidentally on pathologic analysis for cholecystectomy or is found incidentally at the time of surgery for unrelated conditions. Common methods of spread include direct extension, nodal metastases, peritoneal dissemination, and distant metastases. In an autopsy series, the rate of lymphatic involvement was found to be >90% and of hematogenous and peritoneal metastases was 60%-80%. Furthermore, the increased rate of peritoneal spread warrants strong consideration of staging laparoscopy before undergoing curative resection. In terms of local invasion, hepatic infiltration into segment IVB and V occurs in 60% of patients on autopsy studies, given the lack of serosal covering at these sites. Nodal spread to cystic or periholecdochal nodes often occurs first, followed by portal vein, common hepatic, then retropancreatic nodes, and ultimately celiac, superior mesenteric, and aorto caval nodes.

The only curative therapy for gall bladder cancer remains surgical resection, with the extent of resection dictated by tumor stage. T1aN0 tumors can be removed with simple cholecystectomy if negative margins are achieved as high rates of survival near 100% are observed for this group of patients. For higher-stage disease (T1b or greater and node positive), a complete oncologic resection is required, which includes cholecystectomy, en bloc hepatic lobe IVB and V resection, and nodal resection of the porta hepatis (portal vein, hepatic artery, and common hepatic duct), gastrohepatic ligament, port sites, and retrooduodenal regions. Excision of the common bile duct (CBD) can be performed if necessary to remove disease, but it should not be done routinely. R0 resection is an important prognostic factor, and R0 resections are consistently shown to be associated with long-term survival. Thus, re-resection to achieve R0 status may be reasonable. However, even with oncologic resection, the locoregional recurrence rates can be greater than 50%, with mortality due to local progression. Thus, adjuvant therapy for gall bladder cancer should be considered. Table 1 reviews numerous studies of adjuvant therapy in gall bladder cancer.

Adjuvant Chemotherapy

Based on patterns of failure data, there is a strong need for effective systemic therapy in gall bladder cancer. In a retrospective study after curative resection, first recurrence involved a distant site (with or without locoregional recurrence) in 85% of gall bladder cancer cases compared with 40% of cholangiocarcinoma cases. However, randomized phase III (level I) evidence is scarce for this disease. With regard to adjuvant chemotherapy, studies have provided inconclusive results in determining whether there exists a clear benefit. Single-agent adjuvant chemotherapy in gall bladder and BTCs commonly uses agents used for other gastrointestinal cancers, including 5-fluorouracil (5FU), capecitabine, and gemcitabine. Although beyond the scope of this review, numerous phase II studies also support multiple combinations, including gemcitabine-capecitabine, gemcitabine-oxaliplatin, capecitabine-cisplatin, capecitabine-oxaliplatin, 5FU-oxaliplatin, and 5FU-cisplatin. A phase III multi-institutional trial compared a postoperative regimen of mitomycin C (MMC) and 5FU to observation in 118 patients with bile duct cancer and 112 patients with gall bladder cancer. For patients with bile duct cancer, there was no improvement in survival noted. However, for patients with gall bladder cancer, the 5-year OS and DFS rates were significantly improved with adjuvant MMC-5FU chemotherapy (OS 26.0% vs 14.4%, P = 0.04; DFS 20.3% vs 11.6%, P = 0.02). The authors concluded that adjuvant chemotherapy may benefit patients with gall bladder cancer, particularly for those with noncurative resections.

In a large retrospective study of more than 430 patients with gall bladder cancer treated at Memorial Sloan-Kettering Cancer Center from 1995-2005, 123 patients underwent curative resection, and only a minority of these patients received adjuvant therapy, of which 13% received adjuvant chemotherapy with or without
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Abbreviations: CP, cisplatin; DSS, disease-specific survival; GEM, gemcitabine; LRC, local-regional control; Med FU (mo), median follow-up in months; MVA, multi-variate analysis; N, number of patients; NA, not available; NS, not significant; Obs, observation. Unless otherwise specified, rates of LRC, DFS, and OS are crude rates.
Adjuvant CRT Therapy

Adjuvant CRT (most commonly using 5FU-based chemotherapy and EBRT) has also shown improvement in regional control and survival in retrospective studies. In a study on 117 patients by Balachandran et al, 14 adjuvant CRT and T category were the only independent predictors of long-term survival beyond 2 years in multivariate analysis. For patients receiving adjuvant therapy, median survival was 24 months, as compared with 11 months in those without adjuvant therapy (odds ratio \( OR \) 5.54 with no adjuvant CRT, \( P = 0.001 \)). The difference was most pronounced in patients with node-positive stage III disease or those patients who only underwent a simple cholecystectomy (\( P < 0.001 \)). In another study on 73 patients who underwent R0 resection at the Mayo Clinic, Gold et al found no significant differences in patients receiving adjuvant CRT vs those who did not, with a median survival of 4.8 vs 4.2 years. However, patients who received adjuvant CRT had more advanced disease, and after adjusting for T and N category and histopathologic diagnosis, adjuvant CRT was a significant predictor of improved survival in multivariate Cox analysis (hazard ratio 0.3, \( P < 0.001 \)).

Wang et al conducted a companion SEER-based analysis of patients with resected gall bladder cancer from 1995-2005, with the focus on determining the benefit from adjuvant chemoradiotherapy. In this study of 117 patients, propensity score weighting was used to balance the different clinical factors, followed by multivariable regression modeling. Patients with T2-T4 N1 disease, or both benefited from adjuvant CRT with regard to survival. Nomograms and a browser-based online software program (http://skynet.ohsu.edu/nomograms) have been established from this study for practitioners to predict the benefit of adjuvant CRT after gall bladder cancer resection for an individualized patient.

Cholangiocarcinoma

The incidence of cholangiocarcinomas is 3000-4000 cases per year in the United States, with incidence rising globally. Cholangiocarcinomas are classified as intrahepatic (IHCC) and extrahepatic (EHCC) in origin. EHCC is further subdivided into perihilar (Klatskin) tumors and CBD tumors above the ampulla of Vater. Perihilar tumors are those arising at or near the confluence of the right and left hepatic ducts. CBD tumors can arise from the proximal, middle, and distal portions of the CBD. Based on SEER data between 1992 and 2000, EHCC and IHCC had similar diagnosis rates (49% vs 51%), however, the true incidence is difficult to determine because of variations in International Classification of Diseases (ICD) coding and distribution of local geographic risk factors, in addition to genetic differences among various populations. Klatskin tumors are the most common EHCC subtype and occur in 60%-70% of cases with distal cholangiocarcinoma in 20%-30% of cases. Risk factors for cholangiocarcinoma may include biliary calculi, choledochal cysts, liver flukes, tape worms, history of thorotrust, hepatitis B and C, human immunodeficiency virus, and primary sclerosing cholangitis. As with gall bladder cancer, it appears that any condition causing chronic inflammation of the biliary tract is likely a predisposing risk factor. Most cholangiocarcinomas are adenocarcinomas (>90%), with rare histologies including sarcomas, lymphomas, small cell carcinomas, and squamous cell carcinomas.

As with gall bladder cancer, cholangiocarcinomas often present with advanced disease. Typically, intrahepatic tumors present with abdominal pain whereas extrahepatic lesions more commonly present with biliary obstruction. A major
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difference in IHCC and EHCC is resectability. IHCC and proximal EHCC are more difficult to excise with adequate negative margins because of variations in the amount of liver parenchyma involved. Consequently, survival is compromised. The main curative treatment remains surgery, with the goal of achieving negative margins (R0), as R0 resection has been shown to correlate with improved survival in both IHCC and EHCC. Unfortunately, the advanced nature of the disease at presentation often precludes a margin-negative resection. After surgery, local-regional recurrence is a predominant pattern of failure even with R0 resection and is more common than in gall bladder cancer. As local failure can be associated with liver failure and death, this argues for adjuvant radiation and CRT to prevent local recurrence. However, as with gall bladder cancer, there is a dearth of prospective or randomized data clearly establishing the benefit of adjuvant therapy. There are numerous retrospective studies, with some results demonstrating a benefit whereas others do not. We summarize some of the key studies in the following sections on IHCC and EHCC as well as in Table 2.

### Intrahepatic Cholangiocarcinoma

Surgery remains the curative treatment for this disease, and it often entails major hepatic resection. When resection is performed, the goal of surgery is to achieve negative margins (R0), which can also include major bile duct resection if necessary. IHCC appears to have a higher risk of nodal involvement than EHCC, with common nodal basins including the hepatoduodenal ligament, peripancreatic, left gastric, pericholedochal, and portal hepatis regions. Thus, lymphadenectomy is commonly performed at the time of surgery. Pathologic factors that predict increased rates of recurrence and worse outcomes include multiple hepatic tumors, nodal involvement, and vascular invasion, which is reflected in the current American Joint Committee on Cancer (AJCC) 7th edition staging system.

### Adjuvant Chemotherapy

Studies testing the role of adjuvant chemotherapy in IHCC are limited. However, the aforementioned phase III trial testing postoperative MMC and 5FU did include a large subset of patients with BTC, but the benefit was restricted to patients with gall bladder cancer. Thus, there are little data supporting the role of adjuvant chemotherapy for IHCC.

### Adjuvant RT

In the largest study on adjuvant radiation for IHCC, more than 3800 patients were analyzed from the SEER database. Adjuvant RT was associated with a survival improvement over observation, with a median survival of 11 months for patients receiving adjuvant radiation compared with 6 months for those who were observed (P = 0.014). After propensity score adjustments for age, race, stage, and year of diagnosis, the authors still found significant improvements with adjuvant radiation (hazard ratio = 0.82) compared with observation.

| Study | Population | Follow-up | RT | Observation | Details | Survival
|-------|------------|-----------|----|-------------|---------|---------|
| Shinohara et al | IHCC (proximal and distal) | 1973-2003 | 30 | 60 | SEER analysis | 26 vs 25 (P = NS) | 53 vs 23 (P = NS)
| Nelson et al | EHCC | 1992-2006 | 45 | 60 | Neoadjuvant CRT (27%) vs adjuvant CRT (73%) | 78 overall | 60
| Fuller et al | EHCC | 1973-2005 | 1569 | Median follow-up not provided | SEER analysis | 78 overall | 34 overall | 53 vs 23 (P = NS)

**Abbreviations:** CC, cholangiocarcinoma; GEM, gemcitabine; LRC, local-regional control; Med FU (mo), median follow-up in months; N = number of patients; NA, not available; NS, not significant; Obs, observation; PFS, progression-free survival. Unless otherwise specified, rates of LRC, DFS, and OS are crude rates.
Adjuvant CRT Therapy
No single study provides guidance on the role of adjuvant CRT in IHCC. In a study by Serafini et al, 92 patients with either EHCC or IHCC were treated with observation or mostly adjuvant CRT. Adjuvant therapy showed a trend toward improved survival compared with observation (median survival 42 vs 29 months, $P = 0.07$). However, only patients with distal EHCC appeared to benefit.

Extrahepatic Cholangiocarcinoma
As with other tumors in the biliary tract, complete resection is the primary mode of curative treatment. Although surgical resection is most commonly used for most cases of resectable EHCC, some tumors in highly selected patients may be amenable to transplantation. In fact, there are data that suggest that with an intensive preoperative regimen of CRT and brachytherapy followed by transplantation, the transplantation can result in better outcomes compared with resection. However, this retrospective study compared 2 treatment groups with considerable differences in patient characteristics. The location of the primary EHCC dictates the type of resection. Specifically, tumors of the proximal one-third of the extrahepatic biliary tree require hilar resection, with en bloc liver resection, lymphadenectomy, and possibly caudate lobe resection. Resection of tumors of the middle one-third entails major bile duct excision and lymphadenectomy, with frozen margin assessment to ensure adequate margin proximally and distally. Lastly, tumors of the distal one-third require pancreaticoduodenectomy and lymphadenectomy, similar to an adenocarcinoma of the pancreatic head. Locoregional recurrence is the predominant site of initial failure. Despite this, the role of adjuvant CRT and RT has been more controversial in EHCC compared with gall bladder cancer.

Adjuvant Chemotherapy
As mentioned, there is a lack of data regarding the role of adjuvant chemotherapy alone. In the randomized trial published by Takada et al, patients who underwent curative resection received infusional 5FU and MMC for 2 cycles, followed by maintenance Xeloda. Chemotherapy showed a nonsignificant improvement in 5-year OS from 28%-41% ($P = 0.48$) for patients with BTC, but a significant improvement for patients with gall bladder cancer. A retrospective single-institutional study examined the role of additional adjuvant chemotherapy after adjuvant CRT 31 and showed significant improvement in 3 year DFS (45%) and OS (61%) compared with adjuvant CRT alone (DFS 27%, $P = 0.04$; OS 31%, $P < 0.01$). The survival benefit was highest in patients with R1 resection and positive lymph nodes.

Adjuvant RT
There are multiple retrospective studies supporting adjuvant radiation in EHCC. Gerhards et al 32 reported on 91 patients with resected hilar cholangiocarcinoma, where 78% were treated with adjuvant radiation. Radiation consisted of EBRT or a combination of EBRT and IORT. Patients receiving radiation had a substantial improvement in median survival (24 vs 8 months, $P < 0.01$). In another study by Todoroiki et al, 33 29 patients were treated with a combination of postoperative IORT and EBRT, IORT alone, or EBRT alone. Compared with 20 patients not receiving adjuvant radiation, postoperative radiation resulted in significantly improved median survival (32 vs 20 months, $P = 0.01$). Furthermore, postoperative radiation resulted in significantly reduced locoregional failure rate (20% vs 69%). In a study on 129 patients with resected EHCC by Schoenthaler et al, 34 35% of patients received EBRT, 17% received charged particles, and 48% underwent observation. Median survival was improved with either EBRT (11 months) or charged particles (14 months) compared with observation (6.5 months, $P < 0.01$).

A SEER analysis conducted by Fuller et al consisted of more than 1500 patients and found no significant differences in outcomes for patients receiving radiotherapy compared with those who did not. However, median survival was equivalent between those receiving total or radical resection vs those receiving subtotal or debulking surgery in combination with radiation (<25 months). Those patients who received subtotal or debulking surgery without radiation had inferior survival (21 months), suggesting that radiation can compensate for subtotal resection. Another SEER analysis of patients with resected EHCC included more than 4700 patients and found that adjuvant radiation over surgery alone resulted in significantly improved median survival compared with surgery alone (15 vs 9 months, $P < 0.0001$). Both of these SEER analyses provide support for adjuvant radiation.

On the contrary, other studies have not shown benefit with adjuvant radiation in EHCC. In a prospective study by Pitt et al, 31 patients with hilar cholangiocarcinoma underwent oncologic resection with 14 receiving adjuvant irradiation to median dose of 54 Gy. The OS was not improved with the addition of radiotherapy (14 vs 15 months). In another study of 69 patients with hilar cholangiocarcinoma, 57% received adjuvant radiation whereas 43% did not. There was no significant difference in median survival between those receiving adjuvant radiation vs those under observation (23 vs 20 months).

Adjuvant CRT Therapy
In a retrospective review by Nakaebe and Pitt of 44 patients with EHCC, IHCC, or gall bladder cancer, 5FU-based CRT improved median survival to 16.4 months as compared with chemotherapy alone (10.7 months) or radiotherapy alone (7.8 months).
months). Another retrospective study on 65 patients by Borghero et al.\textsuperscript{40} showed an advantage of CRT in high-risk patients treated adjuvantly. They compared patients with R0 or node-negative status who were treated with observation compared with patients with R1 or node-positive disease who were treated with 5FU-based CRT. Despite the higher-risk prognostic factors in those treated with CRT, local-regional control, median survival, and 5-year OS rates were not

Figure 2  Representative axial, coronal, and sagittal images of a patient treated with adjuvant chemoradiation for pT2bN0 perihilar extrahepatic cholangiocarcinoma. Patient had a gross total resection and received external-beam irradiation with 45 Gy in 1.8 Gy/fx to tumor bed, liver margin, and regional nodal basins with sequential integrated boost to the tumor bed to a dose of 52.5 Gy in 2.1 Gy/fx concurrent with infusional 5FU. IMRT planning was used with 9 fields and 6-MV photons. Colorwash isodose lines displayed, with PTV for 45-Gy dose depicted as thick red line and PTV for 52.5-Gy dose depicted as thin red line. PTV, planning target volume.
For review only
(typically Ir-192) inserted through a percutaneous transhepatic biliary catheter into the biliary duct can also deliver high-dose focal irradiation with limited regional dose. The dose commonly used is 15-20 Gy prescribed to 0.5-1 cm from the source, generally over 2-3 treatments. However, ILBT does increase the risk of cholangitis and bleeding due to inserting foreign catheters into the biliary tract. Indeed, there is some evidence that ILBT may have detrimental effects on survival compared with adjuvant EBRT alone in a study, highlighting the need for judicious and experienced application of this technology.

Normal tissue constraints that limit dosage include liver, bile ducts, small bowel, stomach, kidneys, and spinal cord. For whole-liver irradiation, the TD 5/5 (dose resulting in 5% risk of severe complication in 5 years) is 30 Gy. Thus, mean liver dose is usually maintained less than 30 Gy. Overdose of liver can result in radiation-induced liver disease. Kidneys are typically limited to a mean dose less than 18-20 Gy, spinal cord limited to 45 Gy maximum, and small bowel or stomach limited to a maximum of 50-55 Gy. Within the small bowel, the duodenum has a thicker wall and small volumes may be able to tolerate total doses between 55 and 60 Gy in standard fractionation.

Summary

Biliary tract tumors are a rare entity for which standard adjuvant therapy has not been established. Certain prognostic factors including degree of resection, tumor stage, and nodal status can be used to judge the risk of local recurrence and distant recurrence. Nomograms and online calculators may be useful in providing quantitative risk assessments and determining the benefit of adjuvant therapy. For gallbladder carcinoma, adjuvant CRT and chemotherapy have offered promising results and further studies are needed to optimize chemotherapy and radiation regimens. National Comprehensive Cancer Network (NCCN) guidelines continue to recommend adjuvant fluoropyrimidine-based CRT for high-risk patients with T2 or higher category disease, positive margins, or nodal involvement (or alternatively fluoropyrimidine or gemcitabine-based chemotherapy). For cholangiocarcinomas, the tumor location and resectability remain prime factors in disease control, whereas adjuvant chemotherapy and radiation remain more controversial. With IHCC, NCCN recommendations include observation for R0 resection, or some type of adjuvant therapy for R1 or R2 resections. For EHCC, however, R0 patients could receive chemotherapy alone, CRT, observation, or clinical trial, whereas R1 or R2 resections should be treated with fluoropyrimidine CRT (which may include brachytherapy), followed by additional fluoropyrimidine-gemcitabine-based chemotherapy. Although fluoropyrimidine-based chemotherapy is considered standard with radiation, no adjuvant chemotherapy-alone regimen for BTC has been standardized. Results from prospective phase II and III studies (eg, SWOG S0809 and BILCAP) will provide more data regarding adjuvant therapy for BTC. With newer systemic agents, molecular targeted therapy, and more modern radiation techniques (eg, IMRT and charged particles), adjuvant therapy may further improve survival. Further prospective and randomized clinical trials are needed to determine optimal adjuvant therapy regimens for BTC.

References


