Extrahepatic Cholangiocarcinoma:

American Radium Society® (ARS) Appropriate Use Criteria (AUC)

Expert Panel on Extrahepatic Cholangiocarcinoma:

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Summary of Literature Review

Introduction/Background

Approximately 8,000 people are diagnosed with cholangiocarcinoma annually in the United States, and the incidence and mortality are increasing. Extrahepatic cholangiocarcinomas (EHCC) account for approximately 90-95% of all cholangiocarcinomas. EHCC are classified as perihilar (tumors located from the junction of the right and left hepatic ducts to the cystic duct) or distal (from the cystic duct to the Ampulla of Vater). Klatskin tumors involve the junction of the left and right hepatic ducts. Perihilar tumors can be further classified according to the Bismuth-Corlette classification based on the extent of ductal infiltration and resectability.

Cure of EHCC is achieved through surgical resection, but few patients are candidates for resection up front, and there are high rates of both local and distant failure following resection. As a result, neoadjuvant and adjuvant treatment strategies involving chemotherapy and radiation (RT) have been developed in an effort to improve outcomes in patients with EHCC. In recent years, orthotopic liver transplant (OLT) following neoadjuvant therapy has also emerged as an effective treatment strategy for select patients. Treatment for unresectable patients involves chemotherapy, RT, or a combination in appropriately selected patients.

Methodology

The evidence regarding treatment outcomes was assessed using the Population, Intervention, Comparator, Outcome, and Study design (PICOS) framework. For patients diagnosed with Stage I-III EHCC, we sought to evaluate how neoadjuvant and/or adjuvant treatments compared to each other, transplant, surgery alone, or definitive chemoradiation (CRT) in terms of response to therapy, quality of life (QoL), or oncologic outcomes through the assessment of data from prospective Phase II-III trials, meta-analyses, and retrospective studies. Trial size required for inclusion was ≥20 patients. The database search strategy and an associated key to aid its interpretation is noted in Appendix A. An extensive analysis of current medical literature covering 1/1/2012 - 1/28/2022 from peer-reviewed journals indexed in the Ovid Medline database and using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines yielded a comprehensive set of relevant articles. Four authors independently screened the studies and full text articles to determine the final studies included in this review as detailed in the reference selection flow diagram (Appendix B). Any discrepancies between the reviewers were resolved by consensus. A total of 104 articles were identified using the search strategy that met all inclusion criteria. Twenty-three additional studies were included through backward citation searching if they were published prior to 1/1/2012 and significantly contributed to the literature, or if they provided supplemental background information found via PubMed. Study type and quality for these references were assessed via American Radium Society™ (ARS) Appropriate Use Criteria (AUC) methodology (Appendix C). The checklist for confirming the completion of essential elements for PRISMA 2020 systematic review may be found in Appendix D.

Staging and Work-Up

Staging of EHCC is based on the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. Perihilar and distal EHCC are staged separately. The primary tumor stage is based on the extent of liver and vascular involvement, in the case of perihilar tumors, and the depth of invasion and vascular involvement, for distal tumors. The nodal stage is based on the number of involved regional nodes. The initial work-up should include liver function tests. Tumor markers, such as carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), and CA 19-9 are optional, but may be obtained to help differentiate between EHCC and other primary tumors and/or for prognostication. Multiphasic computerized tomography (CT) or magnetic resonance imaging (MRI) with intravenous (IV) contrast of the abdomen and pelvis to characterize the primary tumor should be obtained as well as
a CT of the chest to evaluate for metastases. Cholangiography, preferably with magnetic resonance cholangiopancreatography (MRCP), should also be obtained to evaluate the biliary system. Early surgical consultation to assess for resectability and/or transplant is recommended. Biopsy should be obtained in patients who are not candidates for surgery up front.

**Topic 1/Malignant Biliary Obstruction (MBO) (Variant 1/Variant 2)**

The goal of treatment for MBO is to relieve obstruction. Preoperative obstructive jaundice is a risk factor for postoperative mortality in patients undergoing major hepatectomy. Selective preoperative biliary drainage of the future liver remnant is utilized to improve the safety of major hepatectomy. There is clear consensus that preoperative biliary decompression is indicated in patients with cholangitis, patients undergoing preoperative chemotherapy, patients with malnutrition related to hyperbilirubinemia, patients with hepatic or renal insufficiency, and patients undergoing portal vein embolization. The role of pre-operative biliary drainage in patients without underlying hepatic dysfunction, malnutrition, cholangitis and sufficient future liver remnant volume is less clear. Endoscopic retrograde cholangiography (ERCP) during initial work-up often identifies a dominant stricture and may be useful as a first therapeutic step. Delineation of the biliary anatomy with CT or MRI with or without MRCP may also be useful in guiding endoscopic interventions.

**Subtopic 1/Drainage**

Drainage can be achieved via a percutaneous or endoscopic nasobiliary approach, or through endoscopic biliary stent placement. Percutaneous biliary drainage is indicated for inoperable patients when endoscopic stent placement is not feasible, although a multi-institutional randomized phase II trial demonstrated increased mortality with this approach compared to endoscopic drainage. Endoscopic nasobiliary drainage is used as a temporizing measure in perihilar cholangiocarcinomas that are not amenable to endoscopic biliary drainage using a self-expandable metallic stent. Although it is clear that patients with MBO benefit from biliary drainage, the optimal method remains unclear as there are no data from randomized controlled trials.

**Subtopic 2/Stents**

The role of biliary tract stenting in patients with operable EHCC has been the subject of debate as benefits of drainage may be limited if stent related complications, such as cholangitis, occur. Several types of stents are available including plastic, metal, self-expanding metal (covered or uncovered), or radioactive stents. Covered stents can prevent tumor ingrowth and reduced stent failure rates, but are thought to have a higher probability of migration. Uncovered self-expanding metal stents can be dilated or stented in the future but cannot be removed, and provide a palliative option. Stents, regardless of type, are associated with a risk of infection. Antibiotics or removal and/or exchange of stents can be used in case of infection. Prospective data demonstrate improved duration of stent patency and lower cholangitis rates when using metal versus plastic stents. Data suggest decreased stent occlusion and tumor ingrowth using covered stents compared to uncovered stents. Studies are limited by poor life expectancy in patients with MBO and the type of stent remains at the discretion of the interventionist.

**Subtopic 3/Radioactive Stents**

Another method of preventing tumor overgrowth after stenting is through the use of RT. Studies comparing biliary stents with or without implantation of $^{125}$I seeds demonstrate longer stent patency, decreased rates of restenosis, and longer survival times, without differences in complication rates.

**Subtopic 4/High Dose Rate Intraluminal Brachytherapy**

Radiation using $^{192}$Ir high dose rate (HDR) intraluminal brachytherapy (HDR ILBT) delivered after endoscopic placement of a catheter at the site of obstruction can also be used. Studies evaluating efficacy of HDR ILBT demonstrate longer stent patency and improved overall survival (OS) compared...
External beam radiation (EBRT) following stent placement has been shown to improve stent patency compared to stent alone and retrospective data suggests that this approach results in improved local control and OS.

**Subtopic 5/Photodynamic Therapy**

Photodynamic therapy (PDT) using light activation during endoscopy has also been used alone or in combination with other therapies to treat tumor and increase stent patency duration. Single institution prospective randomized trial data for unresectable BTC patients undergoing stent with or without PDT suggested survival and quality of life benefits for this approach compared with stent alone. Three meta-analyses comparing PDT plus a stent vs stent only or other treatment modalities demonstrated improved OS with the addition of PDT. Patients receiving PDT also had improved, biliary drainage, quality of life, and performance scores and in one study PDT (with or without chemotherapy) was associated with an OS benefit.

**Subtopic 6/Radiofrequency Ablation**

Intraluminal radiofrequency ablation (RFA) can also be used in the palliative treatment of MBO. Non-randomized case-controlled and randomized studies demonstrate the efficacy of RFA in improving stent patency times.

**Subtopic 7/Hepatic Arterial Infusion**

Lastly, stent placement with hepatic arterial infusion (HAI) alone or combined with other therapies can be considered. Large retrospective studies have shown improved OS when combining HAI with systemic chemotherapy compared to either modality alone. Single institution data has demonstrated safety and promising results when combining HAI with RT for unresectable EHCC. A large multicenter retrospective study compared outcomes for stent placement with HAI and RFA versus stent alone and demonstrated longer median stent patency and survival times for the combination group versus the control group, without differences in adverse events between the two groups.

In summary, treatment of MBO is typically performed using endoscopic or percutaneous drainage, usually with stent placement. Data suggests that additional therapies used in combination with stents such as radioactive stents, HDR ILBT, RFA, PDT or HAI with or without systemic therapy may prolong stent patency time and survival. The decision of when or how to achieve biliary decompression depends on the location of obstruction and patient condition.

**Topic 2/Surgical Treatment Approaches**

**Subtopic 1/Preoperative Assessment and Determining Criteria for Resectability**

* Surgical Assessment

Cross sectional imaging with high-resolution triphasic CT scan and/or contrast enhanced MRI with MRCP are the imaging modalities of choice to determine resectability of EHCC. Ideally, these studies are obtained prior to biliary drainage, as determination of the biliary and vascular extent of tumor is more challenging after stent placement. Although the biliary mass may be difficult to visualize on imaging, high-quality cross-sectional imaging will provide details about involvement of biliary confluence and anatomic relationship of tumor to the portal vein and hepatic artery. Distal cholangiocarcinomas have higher rates of resectability as compared to perihilar cholangiocarcinomas.

Classification systems are used to provide information about perihilar cholangiocarcinoma local resectability. The primary principle determining resectability is the need for biliary reconstruction and maintaining adequate hepatic parenchyma in the remnant liver. Patients with tumor extending into
bilateral segmental ducts without a target for restoring biliary continuity are unresectable. Similarly, contralateral portal vein involvement and/or lobar atrophy of anticipated remnant liver is considered unresectable.

**Distal Cholangiocarcinoma**

Surgical resection of distal cholangiocarcinoma usually entails a pancreaticoduodenectomy and surgical principles are similar to the management of pancreatic head adenocarcinoma. In the absence of metastatic disease or vascular involvement, the majority of distal cholangiocarcinomas are resectable with pancreaticoduodenectomy. In general, neoadjuvant therapy should be considered in the setting of portal vein involvement in patients who may require portal vein resection with reconstruction (see neoadjuvant therapy section).

**Perihilar Cholangiocarcinoma**

Operative resection of perihilar cholangiocarcinoma is more challenging with higher rates of unresectability and usually requires formal hepatectomy or extended hepatectomy with biliary reconstruction. Therefore, evaluation includes the patient’s functional status and the technical resectability of the tumor, as well as the volume and function of the future liver remnant. An inadequate volume or function of the liver remnant can lead to postoperative hepatic insufficiency. Volumetric analysis should be performed to calculate the size of the future liver remnant. A liver remnant volume of > 25% is sufficient in a healthy liver, however > 30-40% is recommended in the setting of chronic cholestasis, steatosis, cirrhosis or chemotherapy-induced liver toxicity.

Patients with a small future liver remnant volume should be considered for portal venous embolization prior to curative intent resection. Portal vein embolization occludes the portal vein to the side of the liver that is being resected and causes resultant hypertrophy of the future liver remnant. Contralateral lobar hypertrophy occurs over 2-3 weeks and the kinetic growth rate of the future liver remnant is measured. A post PVE kinetic growth rate of > 2% per week has been shown to correlate with decreased rates of hepatic insufficiency and short-term liver specific mortality. Preoperative biliary drainage, as discussed above, should be used to selectively drain the future liver remnant.

Operative resection of perihilar cholangiocarcinoma should begin with diagnostic laparoscopy to rule out peritoneal or liver metastases followed by partial hepatectomy with en bloc resection of the extrahepatic bile duct, portal lymphadenectomy and Roux-en-Y hepaticojejunostomy. In determining whether to proceed with right or left hepatectomy, it should be noted that the right hepatic duct is short (< 1cm) with significant anatomic variability which can add to the complexity of left sided resections. The left hepatic duct is longer (2-3 cm) and follows a more predictable course making a right hepatectomy more straightforward. En-bloc resection of the caudate lobe is typically recommended because tumor typically extends into the caudate lobe via small branches draining into right or left hepatic ducts or the biliary confluence. Lymphadenectomy of locoregional lymph nodes in the hepatoduodenal ligament is recommended but impacts more on staging than on survival. Portal vein resection and reconstruction may be required in some cases to achieve an R0 resection with associated improved OS but increases the complexity of the operation and should only be performed in high volume centers with significant experience with vascular reconstruction. Similarly, hepatic artery resection and reconstruction or combined arterial or venous reconstructions are described but are associated with higher rates of morbidity, mortality and poorer survival rates consistent with a more aggressive disease biology.

**Subtopic 2/Orthotopic Liver Transplantation (OLT)**

OLT has been employed for patients with perihilar cholangiocarcinoma. Compared to resection for patients with small node-negative tumors, OLT is associated with a 33% increase in 5-year OS.
Typically, transplant candidates are surgically unresectable for reasons of either anatomic invasion or underlying patient disease (commonly primary sclerosing cholangitis). However, OLT is limited by inadequate supply of liver allografts to satisfy patient need. Currently, access to deceased donor liver grafts is limited to patients who meet strict criteria defined by the United Network for Organ Sharing. Transplant candidates must demonstrate either ERCP biopsy demonstrating malignancy, CA 19-9 greater than 100U/mL in absence of cholangitis, aneuploidy, or a perihilar mass ≤ 3cm in radial diameter that does not extend below the cystic duct. Patients initially presenting outside of these criteria have significantly worse survival. Patients with EHCC with nodal involvement or distant metastatic disease are not considered transplant candidates. Living donor liver transplantation can be performed more liberally and is determined by institutional protocol. Five-year OS is 68% after liver transplantation.

To maintain transplant eligibility, patients must undergo neoadjuvant therapy. Common protocols include administration of EBRT along with 5-fluorouracil (5-FU) or capecitabine-based chemotherapy. Chemotherapy often continues until transplantation. Survival rates differ amongst patients who develop cancers in the setting of primary sclerosing cholangitis (5-year OS 74%) and patients who develop de novo cholangiocarcinoma (5-year OS 58%). Likewise, patients with no evidence of active disease on post-transplant specimen evaluation have improved survival. As mentioned above, perihilar cholangiocarcinoma is a relatively frequent indication for living donor liver transplantation. Living donor recipients more frequently experience late arterial and portal venous transplant complications compared to other living donor recipients transplanted for other indications. The complications are likely secondary to the administration of neoadjuvant therapy, but do not impact the OS benefit of transplantation.

In summary, surgery is the mainstay of treatment for resectable EHCC. Resectability is primarily determined by the need for biliary reconstruction and maintaining an adequate remnant liver. Distal cholangiocarcinomas are managed with pancreaticoduodenectomy. If there is portal vein involvement, neoadjuvant therapies are recommended. Perihilar cholangiocarcinoma is managed with hepatectomy and biliary reconstruction. A PVE may be indicated in patients with a small future liver remnant. Patients with anatomically unresectable disease should be considered for OLT following neoadjuvant therapy.

**Topic 3/Neoadjuvant Therapy** (Variant 1/Variant 3/Variant 4)

**Subtopic 1/Neoadjuvant Chemotherapy Prior to Surgery**

While surgical resection is the only cure for EHCC, most patients present with advanced disease involving vasculature or direct organ extension that precludes upfront resection. There is a paucity of data regarding the benefit of neoadjuvant chemotherapy and treatment algorithms are frequently extrapolated from the locally advanced/metastatic setting. Nonetheless, such approaches have yielded a downstaging effect that can lead to surgical resection in some patients. In a single institution retrospective study, Kato reported 22 patients with initially unresectable locally advanced biliary tract cancer (BTC) who received neoadjuvant gemcitabine-based chemotherapy. Eight (36.4%) of 22 patients underwent surgical resection. Patients who underwent surgical resection had a significantly longer survival compared with those unable to undergo surgery. In another similarly designed study, Kuriyama stratified 72 patients into resectable (29), borderline resectable (23) and locally advanced cholangiocarcinoma (20). Neoadjuvant chemotherapy with gemcitabine and S-1 was administered. Forty-seven (65.3%) received neoadjuvant chemotherapy including 8 resectable, 21 borderline resectable, and 18 locally advanced. Fifty nine patients (68.1%) underwent curative-intent surgery including 26 resectable, 17 borderline resectable, and 6 locally advanced. Five-year DSS was 31.5%.
(median: 33.0 months): for resectable disease 50.3% (median not reached), and for borderline resectable 30.0% (median 31.4 months). Among 49 patients who underwent resection, DSS was 43.8% (57.0 months): for resectable 57.6% (median not reached), for borderline resectable 41.0% (median 52.4 months), and for locally advanced 0% (median 49.4 months) compared to 23 patients without resection (median 17.2 months).

Neoadjuvant chemotherapy results in increased rate of R0 resection which is an independent prognostic marker for long term survival. In a single arm Phase II trial by Matsuyama, 60 patients with borderline resectable perihilar cholangiocarcinoma received Gemcitabine/S1 for 3 cycles every 21 days followed by surgery. Resection with curative intent was performed in 43 of 60 patients (72%) and amongst those, R0 resection was achieved in 81%. OS was 55.8 months in resected group vs 36.4 months in unresectable group.

**Subtopic 2/Neoadjuvant Chemoradiation Prior to Surgery**

Limited data suggest that neoadjuvant CRT may improve locoregional control and survival by helping to facilitate margin-negative resection (R0), clearance of microscopic locoregional disease spread, and selecting optimal surgical candidates. Jung reported a multi-institutional retrospective series of 57 patients with perihilar cholangiocarcinoma comparing up-front surgery (n=45) vs. neoadjuvant CRT (n=12) to 45-50.4 Gy with concurrent 5-FU or gemcitabine. All 12 patients who received neoadjuvant CRT had locally advanced disease with vascular involvement which prohibited curative-intent surgery. The neoadjuvant CRT group had higher rates of R0 resection (83% vs. 67%) and lower rates of pathologic lymph node involvement (25% vs. 56%), without increased risk of post-operative complications. DFS and OS were comparable between groups, despite notable cohort imbalances.

Kobayashi reported a prospective phase 1 trial of 25 patients with biliary cancers (96% EHCC; 4% gallbladder carcinoma) treated with neoadjuvant CRT to 50-60 Gy, targeting the gross primary tumor and regional lymphatics, with concurrent gemcitabine. The trial demonstrated feasibility of CRT, a high rate of R0 resection (96%), and favorable 3-year OS of 75%. Subsequently, Kobayashi performed a retrospective comparison of 106 patients treated with up-front surgery (n=79) or neoadjuvant CRT (n=27). Neoadjuvant CRT was associated with improved local recurrence (19% vs. 41%), 3-year DFS (78% vs. 58%), and 3-year OS (85% vs. 69%).

**Subtopic 3/Neoadjuvant Chemoradiation Prior to OLT**

Initial series evaluating OLT as curative-intent therapy for unresectable perihilar cholangiocarcinoma were disappointing with 5-year OS of approximately 20-30% and disease recurrence rates of 50-80%. Based upon prior experiences showing efficacy of EBRT and ILBT for biliary cancers, Mayo Clinic developed a protocol of neoadjuvant EBRT 5-FU-based concurrent CRT to a dose of 45 Gy in 1.5 Gy twice-daily fractions followed by ILBT and maintenance capecitabine prior to OLT. Eligible patients had anatomically unresectable perihilar cholangiocarcinoma, radial tumor diameter ≤ 3 cm, no evidence of intra- or extrahepatic disease, no prior abdominal surgeries or transperitoneal biopsies which may violate the tumor planes or seed tumor, and sufficient functional status for transplantation.

In an early report of 56 patients, 28 underwent OLT (50%), and actuarial 5-year OS was 54% for the entire cohort. Amongst those who underwent OLT, the 1- and 5-year OS were 88% and 82%. A multi-institutional study from 12 transplant centers including 287 patients treated with this regimen between 1993-2010 demonstrated 2- and 5-year OS of 68% and 53%, and amongst those who underwent OLT, 2- and 5-year RFS of 78% and 65%. Favorable outcomes have since been replicated.
internationally thus demonstrating feasibility, broader generalizability, and effectiveness of this
treatment strategy.\textsuperscript{54-56} Subsequent meta-analysis including 20 studies and 428 patients who underwent
OLT for unresectable perihilar cholangiocarcinoma demonstrated improved 3-year (66\% vs. 48\%) and
5-year (65\% vs. 32\%) OS for patients treated with neoadjuvant CRT prior to OLT vs OLT alone.\textsuperscript{57}
Recent series have also shown promising early results with the use of SBRT prior to OLT for select
patients.\textsuperscript{38,58,59}

In summary, for select patients with locally advanced disease, neoadjuvant chemotherapy or
CRT may downstage patients to facilitate a curative-intent operation, decrease the risk of margin-
positive resection, improve locoregional control, and potentially improve OS. For anatomically
unresectable patients with perihilar EHCC fulfilling strict selection criteria, neoadjuvant CRT followed
by OLT is a highly effective treatment option.

**Topic 4/Adjuvant Therapy** (Variant 1/Variant 3/Variant 5/Variant 6/Variant 7)

Following complete surgical resection, patients with EHCC remain at high risk for both local and
distant failure, providing the rationale for the use of adjuvant therapy with chemotherapy, RT, CRT, or
some combination. Owing to the rarity of the disease, there remains a lack of randomized phase III data
to guide decisions as far as the optimal adjuvant treatment, in particular with respect to RT.\textsuperscript{60} A number
of single institution retrospective studies and a multicenter retrospective study have suggested an
improvement in OS for patients with resected cholangiocarcinoma who undergo any adjuvant therapy
versus observation alone, in particular for patients with positive surgical margins or positive lymph
nodes.\textsuperscript{61-66}

Several meta-analyses support adjuvant therapy for resected disease. A meta-analysis of 20
studies involving 6,712 patients with BTC undergoing resection with and without adjuvant therapy
found that there was a non-significant improvement in OS with any adjuvant therapy compared with
surgery alone (pooled OR, 0.74; P = .06). Those receiving adjuvant chemotherapy or CRT derived
statistically greater benefit than RT alone (OR, 0.39, 0.61, and 0.98, respectively; P = .02) and the
greatest benefit for adjuvant therapy was in those with node-positive (OR, 0.49; P = .004) and R1 (OR,
0.36; P = .002) disease.\textsuperscript{67} A systematic review and meta-analysis including 42,917 patients from 35
clinical studies found that there was a significant improvement in OS with any adjuvant therapy after
surgery compared with surgery only (HR 0.74; 95\% CI, 0.67 to 0.83; P < 0.001); there was a significant
benefit for adjuvant therapy in those with margin positive surgery (RR, 0.83; 95\% CI, 0.77 to 0.91; P<0.001) and node-positive disease (RR 0.82; 95\% CI 0.76 to 0.89; P < 0.001).\textsuperscript{68} A more recent
systematic review including 14,646 patients from 22 studies assessing the role of adjuvant therapies in
patients with BTC found that gemcitabine was the optimal adjuvant therapy for 5-year OS compared
with CRT (HR = 0.59; 95\% CI = 0.34-0.97), observation (HR = 0.49; 95\% CI = 0.33-0.73), and RT
alone (HR = 0.40; 95\% CI = 0.22-0.71); adjuvant RT either alone or with concurrent chemotherapy
improved OS in patients with positive margins (HR = 0.69; 95\% CI = 0.49-1.00) or positive lymph
nodes (HR = 0.22; 95\% CI = 0.074-0.66).\textsuperscript{69}

**Subtopic 1/Adjuvant Radiation**

Approximately 40\% of patients with cholangiocarcinoma who do not receive adjuvant RT
experience a local failure following surgery, prompting investigations into the role of adjuvant RT for
resected EHCC.\textsuperscript{70} Results from a number of retrospective multi- and single- institution studies have
shown that adjuvant RT improves DFS and LR rates when compared to observation,\textsuperscript{71,72} but inferior OS
when compared to other adjuvant therapies.\textsuperscript{73} While an NCDB analysis found that after propensity score
matching, adjuvant RT was associated with improved median OS (29.3 vs 26.8 months p < 0.001)
irrespective of nodal and margin status in patients with resected distal cholangiocarcinoma,\textsuperscript{74} a SEER
database study with propensity score matching failed to show an OS benefit to adjuvant RT compared to observation for fully resected perihilar cholangiocarcinoma. A single institution retrospective study of patients with an R1 resection failed to find a benefit to adjuvant RT versus surgery alone, however, a multi-institution retrospective study found that compared to observation, adjuvant RT improved 3-year DFS and there were significantly more patients with R1 resections in the adjuvant RT group.

A meta-analysis including 21 trials with 1,465 patients with cholangiocarcinoma or gallbladder cancer investigating the impact of adjuvant RT versus no RT found that the 5-year OS was higher in the RT group than in the no RT group (OR = 0.63; 95% CI 0.50-0.81, p = 0.0002), particularly for patients with node- or margin-positive disease. Another meta-analysis showed that adjuvant RT/CRT significantly improved OS for patients overall (HR 0.69, 95% CI 0.48-0.97, P=0.03), but on subgroup analysis the benefit was only seen in patients with R1 resections (HR 0.44, 95% CI 0.27-0.72, P=0.001).

A multi-institution prospective nonrandomized study of 1,475 patients from 14 institutions investigated the role of adjuvant RT in patients with resected EHCC. The authors found that adjuvant RT with or without chemotherapy was associated with improved OS on multivariate analysis (HR = 0.74; 95% CI = 0.63-0.86, P, 0.001). When the adjuvant RT group was separated into RT alone, CRT, and CRT followed by chemotherapy, the greatest benefit was observed in patients treated with CRT followed by chemotherapy (HR, 0.52; 95% CI, 0.41-0.68).

Subtopic 2/Adjuvant Chemoradiation

A number of single institution retrospective reviews have shown that adjuvant CRT improves DFS and OS versus observation. A retrospective NCDB study comparing adjuvant therapy with chemotherapy or CRT to surgery alone found that CRT improved OS compared to adjuvant chemotherapy (HR = 0.82; 95% CI 0.75-0.91) and the survival benefit was independent of margin status (R0: HR 0.88; 95% CI 0.79-0.97; R1: HR 0.49; 95% CI 0.38-0.62). When compared to adjuvant chemotherapy, however, a systematic review and meta-analysis of 12 studies found increased toxicity with no improvement in OS for adjuvant CRT compared to adjuvant chemotherapy alone. The benefit of adjuvant CRT compared to adjuvant chemotherapy or surgery alone may be limited to patients with R1 or R2 resections, however the data is conflicting.

The only multi-institutional, cooperative group prospective, non-randomized, phase II trial assessing the role of adjuvant chemotherapy followed by CRT included patients with both gallbladder cancer and EHCC. The Southwest Oncology Group (SWOG) S0809 trial enrolled 79 patients with resected EHCC or gallbladder cancer who received 4 cycles of adjuvant gemcitabine and capecitabine followed by capecitabine-based CRT (45 Gy to regional lymphatics, 54-59.4 Gy to the tumor bed). Thirty-two percent of patients had an R1 resection. The 2-year OS was 65% for patients overall; 67% following an R0 resection and 60% following R1. Local, distant, and combined recurrence occurred in 18%, 30%, and 11% of patients, respectively. Grade 3 and 4 toxicity occurred in 52% and 11% of patients, respectively.

Subtopic 3/Adjuvant Chemotherapy

The role of adjuvant chemotherapy for resected EHCC has also been studied. The Bile Duct Cancer Adjuvant Trial (BCAT) was a randomized phase III trial comparing Gemcitabine versus observation in 225 patients who underwent resection for bile duct cancers. No difference in OS between the two groups was noted. Negative results were also found for the Phase III PRODIGE 12-ACCORD 18 trial. 196 patients with R0 or R1 resected cholangiocarcinoma were randomized to receive gemcitabine/oxaliplatin vs observation alone. No significant difference in RFS or OS were found. In a systematic review and meta-analysis of 20 studies involving over 6700 patients who underwent
resection of BTC with or without adjuvant therapy, a non-significant improvement in OS was found with any adjuvant therapy compared with surgery alone (pooled OR, 0.74; P = .06), with the greatest benefit for adjuvant therapy was in those with LN-positive (OR, 0.49; P = .004) and R1 disease (OR, 0.36; P = .002).67

Data supporting adjuvant chemotherapy after resected BTC comes predominantly from the Phase III BILCAP study. Four hundred forty seven patients with completely resected BTC were assigned to either capecitabine or observation. Of note, 38% of patients in each arm had an R1 resection. DFS was significantly greater in capecitabine arm in both the intent-to-treat as well as per-protocol analysis. Median OS was 51.1 months in the capecitabine arm and 36.4 months in the observation arm. This difference was significant in the per-protocol analysis but not in the intent-to-treat analysis.92

In summary, based on the data currently available, most patients with resected EHCC would benefit from adjuvant therapy with either chemotherapy using capecitabine alone, per BILCAP, or chemotherapy with gemcitabine and capecitabine followed by capecitabine-based CRT, as per SWOG.

**Topic 5/Unresectable, Non-metastatic (Variant 2/Variant 4)**

The prognosis of patients with unresectable EHCC is very poor and treatment is typically directed at palliation of symptoms related to obstruction.93 While recent advances in both RT and systemic therapies have shown promising results in improving life expectancy for patients, there is a paucity of data to guide management and most of the available evidence is retrospective. The role of ILBT delivered with or without other therapies has been previously discussed. The role of EBRT therapy in the management of patients with unresectable disease remains controversial.

**Subtopic 1/(Chemo)Radiation**

While data suggest that EBRT in conjunction with systemic therapy is superior to best supportive care alone, it does not appear to confer a survival benefit for patients who do not receive any systemic treatment.31,94 Existing data suggest that EBRT delivered with concurrent chemotherapy is superior to both EBRT and chemotherapy alone for unresectable patients.95,96 Thus the combination of systemic chemotherapy with CRT may be the optimal approach for patients with unresectable disease.

The optimal dose and technique for delivering RT has not been determined. A single institution prospective study including 27 patients treated with EBRT with concurrent weekly gemcitabine with or without HDR ILBT boost found the median OS, 2-year OS, and 3-year OS to be 14 months, 27%, and 7%, respectively.97 The role of an HDR ILBT boost remains to be elucidated.98 Another more recent single institution retrospective cohort study of 48 patients with unresectable EHCC treated with CRT found the 2-, 3-, and 5-year OS rates to 33% (95% CI: 22-50%), 20% (95% CI: 11-36%), and 7% (95% CI: 2-20%), respectively, with a median OS of 12 months.99 On univariate analysis, biologically effective dose (BED) >59.5 Gy10 was associated with improved OS [HR: 0.40, 95% CI: 0.18-0.92, P=0.03] and PFS [HR: 0.37, 95% CI: 0.16-0.84, P=0.02], and on multivariate analysis it remained associated with PFS [HR: 0.34, 95% CI: 0.15-0.78, P=0.01], suggesting a benefit to dose escalation for this disease. However, another retrospective series of 80 patients with unresectable EHCC failed to show a benefit to dose escalation.100 Dose escalation using proton beam therapy has been investigated as an alternative to photon therapy. A multi-institution retrospective study of 30 patients with unresectable EHCC treated with proton beam therapy to a median dose of 72.6 Gy found the 1-year local control, regional control, and distant metastases-free rates were 88%, 86%, and 68%, respectively.101 The median OS and PFS were 19.3 and 10.4 months, respectively.
The delivery of ablative doses of RT for unresectable EHCC has also been studied. A single institution prospective single arm study reported a complete response rate at 3 months of 34.9% in patients treated with a hypofractionated regimen of 44-48 Gy in 9-12 fractions. A single institution phase I feasibility study involving 6 patients with unresectable EHCC treated with a hypofractionated regimen of 60 Gy in 15 fractions following 6-8 cycles of systemic chemotherapy found the 12-month LC rate to be 80% without any observed limiting toxicities.

**Subtopic 2/Systemic Therapies**

The pivotal ABC-02 trial was a Phase III study that enrolled 410 patients with locally advanced or metastatic cholangiocarcinoma to receive either cisplatin/gemcitabine vs gemcitabine alone. OS was superior in the combination group without added risk of toxicity. This established gemcitabine/cisplatin as the standard first line treatment for advanced BTC. In patients who are not able to tolerate cisplatin due to chronic kidney disease or hearing impairment, alternative treatment with gemcitabine plus nab-paclitaxel can be considered. Although the single institution phase II trial did not meet its primary endpoint, it was shown to be a safe and well tolerated.

Other combinations with gemcitabine in the first line setting have been evaluated. A trial investigating to addition of sorafenib to gemcitabine versus gemcitabine alone found no benefit to the addition of sorafenib. While Gemcitabine plus S-1 has been shown to have activity compared with gemcitabine alone, S-1 is not currently available in the United States. More recently, the TOPAZ-1 trial showed a modest but significant benefit in OS and PFS with the addition of durvalumab, a PDL-1 inhibitor, in combination with gemcitabine plus cisplatin for first line treatment of advanced BTC.

ABC-06 was the first trial to investigate the role of second line chemotherapy after progression of disease with platinum-based first line therapy. The randomized phase III ABC-06 study showed a statistical OS benefit for second line FOLFOX after progression of gemcitabine plus cisplatin vs best supportive care (OS 6.2 months vs 5.3 months). However, the low response rates of 2nd line chemotherapy has peaked interest in the role of molecularly targeted systemic therapies.

There has been an interest in molecular profiling of cholangiocarcinoma as several key targets have been identified over the last several years. IDH1/2 mutations are found in 10-23% of intrahepatic and 0.8% of EHCCs. A phase III study with 185 patients with advanced IDH1 mutant cholangiocarcinoma, who had progressed on previous therapy were treated with ivosidenib, an IDH1 inhibitor. The study reached its primary endpoint and demonstrated an improvement in PFS 2.7 months in treatment group vs 1.4 months in the observation group (0.37; 95% CI 0.25-0.54; p<0.0001).

Mutations in FGFR2 fusions has shown to be another potential therapeutic target in advanced BTC, although less commonly encountered in EHCC than in intrahepatic cholangiocarcinomas. The FIGHT 202 clinical trial was a phase 2 single arm study that evaluated the safety and efficacy of pemigatinib, an FGFR inhibitor in previously treated patients with advanced BTC. 35.5% patients achieved an objective response.

Other active targets in cholangiocarcinoma include BRAFV600E mutation which was evaluated in a Phase II ROAR trial with 43 patients previously received at least 1 line of therapy. Patients were treated with a BRAF, dabrafenib plus a MEK inhibitor, trametinib with an ORR 51%, median PFS 9 months and OS 13.5 months.

The use of checkpoint inhibition appears to have activity in cholangiocarcinoma tumors who express high tumor mutational burden (TMB-H) or microsatellite instability (MSI-H). Subgroup analysis of the KEYNOTE 158 study investigated the use of pembrolizumab, a PDL 1 inhibitor in
cholangiocarcinoma subgroup revealed a ORR of 40.9% (95% CI 20.7-63.3%), median PFS 4.2 months, OS 24.3 months. Pembrolizumab is currently approved for advanced solid tumors with TMB-H or MSI-H features.

In summary, the optimal treatment of patients with unresectable EHCC remains to be elucidated. Systemic therapy with gemcitabine plus cisplatin is superior to single-agent therapy. RT with concurrent chemotherapy may be added in appropriate patients. Molecularly-targeted agents and check-point inhibitors are being studied in the second-line setting after progression through first-line therapy.

**Topic 6/ Radiation Therapy Dose and Technique**

**Subtopic 1/Simulation**

Patients are simulated supine with arms raised using a custom immobilization device. Respiratory motion should be assessed with a 4-dimensional CT and patients with excessive target motion may be considered for respiratory motion management strategies such as abdominal compression or beam gating strategies such as voluntary breath-hold or respiratory-phase gating. Abdominal CT with intravenous contrast and/or MRI may be registered to the planning CT to assist with target delineation.

**Subtopic 2/Target Volumes**

*Adjuvant*

The most common sites of locoregional recurrence after surgery include the tumor bed and lymph node regions including hepatoduodenal ligament/hepatic hilum, common hepatic, celiac, pancreaticoduodenal, superior mesenteric, and retroperitoneal and these data guide adjuvant RT target volume delineation. In the post-operative setting, any gross residual disease should be contoured as gross tumor volume (GTV). The clinical target volume (CTV) should include the tumor bed based upon pre- and post-operative imaging, surgical clips, and operative reports plus the aforementioned high-risk elective lymph node regions.

When delivered pre-operatively, most series have delineated the CTV as the gross primary tumor plus a 0-1.0 cm margin and inclusion of elective lymph node regions. Histopathologic studies have suggested microscopic disease extension longitudinally along the bile duct for which 90% of cases have disease confined within 1.0-2.0 cm beyond gross tumor. Therefore, larger longitudinal margins can be considered.

*Definitive*

For definitive RT, most series have delineated the CTV as the gross primary tumor plus a 0-1.0 cm margin. Inclusion of elective lymph node regions may be considered as there are data to suggest the incidence of regional recurrence may be as high as 24% after RT without elective lymph node RT. For patients planned for SBRT, most series have contoured the GTV as the gross primary tumor with no additional margin for CTV. An expansion of the CTV by 0.5-1.0 cm radially and 0.5-1.5 cm cranio-caudally is typically applied to generate the planning target volume (PTV). The exception is for SBRT in which marginal expansions have ranged from 0.3-0.5 cm radially and 0.3-0.8 cm cranio-caudally.

**Subtopic 3/Dose and Fractionation**

For post-operative RT, doses of 40-45 Gy in 1.8-2.0 Gy fractions covering the tumor bed and at-risk elective lymph node regions are suggested. For a tumor bed boost to a total dose of 50-54 Gy is recommended after R0 resection and a dose of 55-59.4 Gy is recommended after R1
resection. In general, intensity modulated RT (IMRT) is the preferred technique, which has been shown to result in slightly improved DFS rates with marginal significance compared to conformal 3-dimensional RT.\textsuperscript{125}

For pre-operative RT, doses of 45-60 Gy in 1.8-2.0 Gy fractions are recommended.\textsuperscript{47-49} An alternative regimen, particularly prior to OLT, is 40.5-45 Gy in 1.5 Gy twice-daily fractions, followed by ILBT to a dose of 9.3 Gy with HDR brachytherapy or 20 Gy delivered over 20-25 hours with low dose rate brachytherapy, each prescribed to 1 cm depth.\textsuperscript{52,53,55,56}

For definitive RT, doses of 45-60 Gy in 1.8-2.0 Gy fractions have most commonly been used.\textsuperscript{98-100,121} Hypofractionated regimens of 45-67.5 Gy in 15 fractions and 66-72 Gy in 10-22 fractions have also been used.\textsuperscript{101,103} The most commonly reported regimens for SBRT have included 30-60 Gy in 3-5 fractions.\textsuperscript{38,58,59,120,126,127}

**Summary of Recommendations**

1. The panel recommends strongly that adjuvant/neoadjuvant chemotherapy or CRT is usually appropriate for the typical case with a stage III resectable perihilar cholangiocarcinoma.
2. The panel recommends strongly that chemotherapy followed by CRT is usually appropriate for the typical case with unresectable mid bile duct carcinoma.
3. The panel recommends strongly that adjuvant/neoadjuvant chemotherapy or CRT may be appropriate for the typical case with resectable node-positive perihilar cholangiocarcinoma encasing the portal vein.
4. The panel recommends strongly that neoadjuvant CRT followed by orthotopic liver transplant may be appropriate for the typical case with stage I perihilar cholangiocarcinoma involving the common hepatic duct in a patient with primary sclerosing cholangitis.
5. The panel recommends strongly that observation or adjuvant chemotherapy is usually appropriate for the typical case with stage I (node negative) perihilar cholangiocarcinoma resected to negative margins.
6. The panel recommends strongly that adjuvant chemotherapy or CRT is usually appropriate for the typical case with resected perihilar cholangiocarcinoma with multiple positive margins.
7. The panel recommends strongly that adjuvant chemotherapy alone or chemotherapy followed by CRT is usually appropriate for the typical case with node-positive perihilar cholangiocarcinoma resected to negative margin.

**Summary of Evidence**

This section summarizes the references on the evidence table.

Of the 127 references cited in the ARS Appropriate Use Criteria Extrahepatic Cholangiocarcinoma document, 124 are categorized as therapeutic references including 14 well-designed studies, 48 good quality studies, and 65 quality studies that may have design limitations.

There are 4 references that may not be useful as primary evidence. There are 14 references that are meta-analysis studies.

The 127 references cited in the ARS Appropriate Use Criteria Extrahepatic Cholangiocarcinoma document were published from 1946 to 2010.

Although there are references that report on studies with design limitations, 48 well-designed or good quality studies provide good evidence.
The American Radium Society™ Appropriate Use Criteria and its expert panels have developed criteria for determining appropriate procedures for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide treating and referring physicians in making decisions regarding diagnosis and treatment of cancers and related or associated conditions. Generally, the complexity and severity of a patient’s clinical condition should dictate the selection of appropriate diagnostic procedures or treatments. Only those examinations or treatments generally used for evaluation of the patient’s condition are ranked. Other procedures necessary to evaluate or treat other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate procedures or treatments. Procedures, techniques, or other interventions classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment, applications, and treatment protocols should be encouraged. The ultimate decision regarding the appropriate use of any specific examination or treatment must be made by the referring physician and oncologist in light of all the circumstances presented in an individual examination.
References


