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American Radium Society (ARS) Appropriate Use Criteria (AUC) for Extrahepatic Cholangiocarcinoma

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Abstract: Although uncommon, extrahepatic cholangiocarcinoma (EHCC) is a deadly malignancy, and the treatment approaches remain controversial. While surgery remains the only cure, few patients are candidates for resection up front, and there are high rates of both local and distant failure following resection. Herein, we systematically review the available evidence regarding treatment approaches for patients with EHCC, including surgery, radiation, and chemotherapy. The evidence regarding treatment outcomes was assessed using the Population, Intervention, Comparator, Outcome, and Study design (PICOS) framework. A summary of recommendations based on the available literature is outlined for specific clinical scenarios encountered by providers in the clinic to guide the management of these patients.

Key Words: Extrahepatic cholangiocarcinoma, radiation therapy, chemotherapy, surgery, liver transplant

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Approximately 8000 people are diagnosed with cholangiocarcinoma annually in the United States, and the incidence and mortality are increasing.[1] Extrahepatic cholangiocarcinomas (EHCC) account for ~90% to 95% of all cholangiocarcinomas and 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). Perihilar tumors can be further classified according to the Bismuth-Corlette classification based on the extent of ductal infiltration and resectability.[2]

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 to improve outcomes in patients with EHCC. 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 surgery, with or without neoadjuvant and/or adjuvant treatments, compared with each other in terms of response, quality of life, or oncologic outcomes through the assessment of data from prospective Phase I-III trials, meta-analyses, and retrospective studies. The trial size required for inclusion was ≥ 20 patients. The database search strategy is noted in Supplemental File 1 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A438). An extensive analysis of current medical literature covering January 1, 2012 to January 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.[3] Four authors independently screened the studies to determine those included in this review as detailed in the reference selection flow diagram (Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/AJCO/A439). 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 before January 1, 2012 and significantly contributed to the literature or if they provided supplemental background information found through PubMed. Study type and quality for these references were assessed through American Radium Society (ARS) Appropriate Use Criteria (AUC) methodology (Supplemental Table 1, Supplemental Digital Content 3, http://links.lww.com/AJCO/A440). The checklist for confirming the completion of essential elements for PRISMA 2020 systematic review may be found in Supplemental Table 2 (Supplemental Digital Content 4, http://links.lww.com/AJCO/A441).

Staging and Work-Up

Staging of EHCC is based on the eighth edition of the American Joint Committee on Cancer (AJCC) staging system.[4] Perihilar and distal EHCC are staged separately. The initial work-up should include liver function tests. Although optional, tumor markers, such as carcinoembryonic antigen, alpha-fetoprotein, and CA 19-9, may help differentiate EHCC from other primaries 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 and a CT of the chest to evaluate for metastases. Cholangiography 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.

Management of Malignant Biliary Obstruction (MBO)

The goal of treatment for MBO is to relieve obstruction (Tables 1, 2). Preoperative obstructive jaundice is a risk factor for postoperative mortality in patients undergoing major hepatectomy. Endoscopic retrograde cholangiography (ERCP) during initial work-up often identifies a dominant stricture and may be useful as a first therapeutic step.

Drainage can be achieved through 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 with endoscopic drainage.[5] The optimal method remains unclear due to a lack of randomized data.[6]

Several types of stents are available. Covered stents can prevent tumor ingrowth and reduce stent failure rates but are thought to have a higher probability of migration.[7] Uncovered self-expanding metal stents provide a palliative option. Prospective data demonstrate improved duration of stent patency and lower cholangitis rates when using metal versus plastic stents.[8] Data suggest decreased stent occlusion and tumor ingrowth using covered stents compared with uncovered stents.[9] The type of stent remains at the discretion of the interventionist.

Another method of preventing tumor overgrowth after stenting is with 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.[10–13] 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 the efficacy of HDR ILBT demonstrate longer stent patency and improved overall survival (OS) compared with stent alone.[14–17] External beam RT following stent placement can improve stent patency compared with stent alone,[18] and retrospective data suggest that this approach results in improved local control and OS.[19]

Photodynamic therapy (PDT), using light activation during endoscopy, or intraluminal radiofrequency ablation (RFA), has also been used alone or in combination with other therapies to treat the tumor and increase stent patency duration. Patients receiving PDT have been shown to have improved biliary drainage, quality of life, performance scores, and possibly OS.[20–25] Nonrandomized case-controlled[26] and randomized[27] studies demonstrate the efficacy of RFA in improving stent patency times.

Lastly, stent placement with hepatic arterial infusion (HAI) alone or combined with other therapies can be considered. Retrospective studies have shown improved OS when combining HAI with systemic chemotherapy or RT compared with either modality alone.[28–31] 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 2 groups.[32]

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 may prolong stent patency time and survival. The decision of when or how to achieve biliary decompression depends on the location of the obstruction and the patient condition.

Surgery

Distal cholangiocarcinomas have higher rates of resectability as compared with perihilar cholangiocarcinomas. 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 patients who may require portal vein resection with reconstruction.

Operative resection of perihilar cholangiocarcinoma is more challenging with higher rates of unresectability and usually requires formal hepatectomy or extended hepatectomy with biliary reconstruction. Classification systems are used to provide information about perihilar cholangiocarcinoma local resectability.[33] 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. Therefore, evaluation includes the patient's functional status and the technical resectability of the tumor and the volume and function of the future liver remnant. A liver remnant volume of $>25\%$ is sufficient in a healthy liver; however, $>30\%$ to 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 before curative intent resection.[34] Portal vein embolization occludes the portal vein to the side of the liver that is being resected and causes

TABLE 1. Variant 1: 60 year old female with clinical Stage IIIA, cT2bN2M0 by MRI, hilar cholangiocarcinoma presenting with jaundice, icterus, and hyperbilirubinemia (total bilirubin = 20). Evaluated by surgery and is a candidate for hepatic resection and regional lymphadenectomy. ECOG performance status 1-2. (Case for management of MBO and adjuvant therapy N2)

Treatment	Rating category	Group median rating	Disagree	SQ	SOE	SOR
Treatment Options						
Neoadjuvant biliary drainage for MBO	A	8		1,3	S	↑
Upfront Surgery without biliary drainage	U	3		3	M	↑
Neoadjuvant CT followed by surgery	*M	5	X	3,3,2,2	S	↑
Neoadjuvant RT followed by surgery	U	3		-	EC	↑
Neoadjuvant CRT followed by surgery	M	5.5		3,3,2	S	↑
Surgery followed by adjuvant CT alone	*M	5	X	M,M,2,1	S	↑
Surgery followed by adjuvant RT alone	U	3		3,3,3,3	S	↑
Surgery followed by adjuvant CRT	M	6		3,3,3,3,3,3,3,3,3,3,3,3	S	↑
If RT: Dose to Tumor/Tumor Bed assuming negative margins						
40-45 Gy/20-25 fx	M	5		3,3,3,3,3	S	↑
46-54 Gy /23-30 fx	A	8		3,3,2,3,3,3,3,3,3,2,3,3,3	S	↑
55-60 / 25-33 fx	U	3		3,2,3,3,3,3	S	↑
If RT: Dose to Elective nodes						
40-45 Gy/20-25 fx	A	8		3,2,3,3,3,3,2	S	↑
46-50.4 Gy /23-28 fx	M	5		-	EC	↑
If RT: Volumes to be included in Clinical Target Volume						
Celiac	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
SMA	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
Porta hepatis (hepatoduodenal ligament and common hepatic)	A	8.5		3,2,3,3,3,3,3,3,2,3	S	↑
Pancreaticoduodenal	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
Paraaortic	A	7		3,2,3,3,3,3,3,3,2,3	S	↑
GTV (Neoadjuvant) or Tumor bed + margin (Adjuvant)	A	9		3,2,3,3,3,3,3,3,2,3	S	↑

Abbreviations: - indicates neutral; ↑, strong recommendation; ↓, weak recommendation; A, usually Appropriate; CRT, chemo-radiation; CT, chemotherapy; EC, expert consensus; EO, expert opinion; fx, fraction; L, limited; M, May be appropriate; M, meta-analysis; M, moderate; MBO, malignant biliary obstruction; NA, not applicable; RT, radiation therapy; S, strong; SMA, superior mesenteric artery; SOE, strength of evidence; SOR, strength of the recommendation; SQ, refers to the study quality (1, 2, 3, or 4) of the references listed; U, Usually not appropriate.

*Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

Variant Discussion:

The optimal method of preoperative biliary decompression (endoscopic nasobiliary, endoscopic with stent placement or percutaneous transhepatic) in patients with ECC who present with obstructive jaundice is variable depending on institutional preference. Although the optimal preoperative bilirubin level is a matter of debate, the shortest possible duration of perioperative biliary drainage is recommended. For those patients who are recommended to undergo neoadjuvant therapy, perioperative biliary drainage is strongly recommended. In patients undergoing neoadjuvant therapy, additional measures to maintain biliary patency after drainage (ie stent placement) may be useful. Typically radioactive stent placement, intraluminal brachytherapy, PDT and RFA in addition to biliary drainage to maintain biliary patency are reserved for inoperable ECCs.

Dose to Tumor/Tumor bed may depend of final pathology. Preoperative radiation doses are typically 45 – 50 Gy, sometimes with doses as high as 60 Gy delivered to areas at risk for positive margin using intensity modulated radiation therapy with simultaneous integrated boost technique. Postoperative radiation doses are typically prescribed at 40 – 45 Gy with boost to 50 – 54 Gy for R0 resections and 55 – 59.4 Gy for R1 resections. Available data most strongly support elective node dose of 40 – 45 Gy but it is not unreasonable to consider doses up to 50.4 Gy to control microscopic disease as the panel feels 40 Gy is somewhat low (expert consensus).

resultant hypertrophy of the future liver remnant. Contralateral lobar hypertrophy occurs over 2 to 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.[35]

OLT has been employed for patients with perihilar cholangiocarcinoma. Compared with resection for patients with small node-negative tumors, OLT is associated with a 33% increase in 5-year OS rates.[36] 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 an inadequate supply of liver allografts to satisfy the patient's need. Currently, access to deceased donor liver grafts is limited to patients who meet strict criteria defined by the United Network for Organ Sharing. Patients initially presenting outside of these criteria have significantly worse survival.[37] Living donor liver transplantation can be performed more liberally and is determined by the institutional protocol.[38] Patients with EHCC with nodal involvement or distant metastatic disease are not considered transplant candidates. To maintain transplant eligibility, patients must undergo neoadjuvant therapy. Survival rates differ among patients who develop cancers in the setting of primary sclerosing cholangitis (5-y OS 74%) and patients who develop de novo cholangiocarcinoma (5-y OS 58%).[39] Likewise, patients with no evidence of active disease on post-transplant specimen evaluation have improved survival.

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. Neoadjuvant therapies may be indicated. Patients with the anatomically unresectable disease should be considered for OLT following neoadjuvant therapy.

Neoadjuvant Therapy

While surgical resection is the only cure for EHCC, most patients present with advanced disease that precludes upfront

TABLE 2. Variant 2: 48 year old with clinical Stage IIB, cT4N1M0 mid bile duct carcinoma by MRI, presenting with jaundice, icterus, and hyperbilirubinemia (total bilirubin = 15). Anatomically unresectable. Good performance status. (Case for management of MBO and unresectable disease)

Treatment	Rating category	Group median rating	Disagree	SQ	SOE	SOR
Treatment Options						
Upfront biliary drainage for MBO prior to other therapies	A	8		1,3	S	↑
Neoadjuvant CT followed by re-evaluation for surgery	A	7		3,3,2,2	S	↑
Neoadjuvant CRT followed by re-evaluation for surgery	A	7		3,3,2	S	↑
CRT	M	4		3,3,3,3	S	↑
CT followed by CRT	*M	5	X	3	M	↑
CT Alone	M	6		1,2,1,2,1	S	↑
CT + immunotherapy	M	5		1,2	S	↑
Targeted Therapy	M	4.5		2,2,3	S	↑
Best supportive care	U	3		3,2	M	↑
If RT: Dose to Tumor						
45 - 60 Gy / 25 -33 fx	A	8		3,3,2,3,3,3,3,3,3,3,2,3,3,3,3	S	↑
45-67.5 Gy/ 15 fx	A	7		3	M	↑
40 -50 Gy/ 5 fx SBRT	M	5.5		3,3,3,3	S	↑
51-60 Gy/ 5 fx SBRT	U	3		3	M	↑
If RT: Dose to Elective nodes						
40 - 45 Gy/ 20-25 fx	A	7.5		3,2,3,3,3,3,2	S	↑
46 – 50.4 Gy/ 23-28 fx	M	5		-	EC	↑
If RT: Volumes to be included in Clinical Target Volume						
Celiac	A	7.5		3,2,3,3,3,3,3,3,2,3	S	↑
SMA	M	5		3,2,3,3,3,3,3,3,2,3	S	↑
Porta hepatis (hepatoduodenal ligament and common hepatic)	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
Pancreaticoduodenal	A	7		3,2,3,3,3,3,3,3,2,3	S	↑
Paraaortic	M	5		3,2,3,3,3,3,3,3,2,3	S	↑
Tumor + margin	A	8.5		3,2,3,3,3,3,3,3,2,3	S	↑

Abbreviations: - indicates neutral; ↑, strong recommendation; ↓, weak recommendation; A, usually Appropriate; CRT, chemo-radiation; CT, chemotherapy; EC, expert consensus; EO, expert opinion; fx, fraction; L, limited; M, May be appropriate; M, meta-analysis; M, moderate; MBO, malignant biliary obstruction; NA, not applicable; RT, radiation therapy; S, strong; SMA, superior mesenteric artery; SOE, strength of evidence; SOR, strength of the recommendation; SQ, refers to the study quality (1, 2, 3, or 4) of the references listed; U, Usually not appropriate.

*Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

Variant Discussion:

The optimal method of biliary decompression (endoscopic nasobiliary, endoscopic with stent placement, or percutaneous transhepatic) in patients with ECC who present with obstructive jaundice is variable depending on institutional preference. Additional measures to maintain biliary patency after drainage such as stent or radioactive stent placement, intraluminal brachytherapy, PDT and RFA in addition to biliary drainage are typically reserved for inoperable ECCs.

More aggressive therapy would likely be recommended in patients with good performance status but in patients with poor performance status best supportive care or palliative local therapy may be considered.

SBRT may not be a viable treatment option for lymph node positive ECC unless the lymph node is adjacent to the primary tumor and bowel doses are not limiting. In addition, SBRT total dose would be dependent on ability to meet normal tissue tolerances. Elective nodes would not be included in SBRT target volumes. Hypofractionated radiotherapy may be considered for node positive ECCs that are not candidates for SBRT.

Available data most strongly support elective node dose of 40 – 45 Gy but it is not unreasonable to consider doses up to 50.4 Gy to control microscopic disease as the panel feels 40 Gy is somewhat low (expert consensus).

resection.[40] There is a paucity of data regarding the benefit of neoadjuvant chemotherapy. Nonetheless, such approaches have yielded a downstaging effect that can lead to surgical resection in some patients (Table 3). Single institution retrospective studies have demonstrated improved rates of resectability when patients with upfront unresectable or borderline resectable disease undergo neoadjuvant chemotherapy, with improved OS in resected versus unresected patients.[41,42] Neoadjuvant chemotherapy not only improves resectability but also results in an increased rate of R0 resection, which is an independent prognostic marker for long-term survival.[43] 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 among those, R0 resection was achieved in 81%. OS was 55.8 months in resected group versus 36.4 months in the unresectable group.[44]

Limited data suggest that neoadjuvant CRT may also improve locoregional control and survival by helping to facilitate margin-negative resection (R0), clearance of microscopic locoregional disease spread, and selecting optimal surgical candidates.[45–47] Jung reported a multi-institutional retrospective series of 57 patients with perihilar cholangiocarcinoma comparing up-front surgery (n = 45) versus neoadjuvant CRT (n = 12) 45 to 50.4 Gy with concurrent 5-FU or gemcitabine.[45] 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 postoperative complications. A prospective phase 1 trial of 25 patients with biliary cancers (96% EHCC; 4% gallbladder carcinoma) treated with neoadjuvant CRT demonstrated the

TABLE 3. Variant 3: 72 year old male with clinical Stage IIA, 3.5cm hilar cholangiocarcinoma with prominent hilar adenopathy by MRI, encasing the right portal vein, left hepatic duct uninvolved. Non- metastatic. Good performance status, normal liver function. (Technically resectable disease but with hilar adenopathy)

Treatment	Rating category	Group median rating	Disagree	SQ	SOE	SOR
Treatment Options						
Surgery Alone	U	3		-	EC	↑
Neoadjuvant CT followed by surgery	A	7		3,3,2,2	S	↑
Neoadjuvant RT followed by surgery	M	4		-	EC	↑
Neoadjuvant CRT followed by surgery	A	7.5		3,3,2	S	↑
Surgery followed by adjuvant CT alone	*M	5	X	M,M,2,1	S	↑
Surgery followed by adjuvant RT alone	U	3		3,3,3,3	S	↑
Surgery followed by adjuvant CRT	*M	5	X	3,3,3,3,3,3,3,3,3,3,3,3	S	↑
Definitive CRT	M	4.5		3,3,3,3	S	↑
If RT: Dose to Tumor/Tumor bed						
45 -60 Gy/25 -33 fx	A	8		3,3,2,3,3,3,3,3,3,2,3,3,3,3	S	↑
45-67.5 Gy/ 15 fx	A	7		3	M	↑
If RT: Dose to Elective nodes						
40-45 Gy/20-25 fx	A	8		3,2,3,3,3,3,2	S	↑
46-50.4 Gy /23-28 fx	M	5		-	EC	↑
If RT: Volumes to be included in Clinical Target Volume						
Celiac	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
SMA	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
Porta hepatis (hepatoduodenal ligament and common hepatic)	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
Pancreaticoduodenal	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
Para-aortic	M	5		3,2,3,3,3,3,3,3,2,3	S	↑
Tumor + margin	A	9		3,2,3,3,3,3,3,3,2,3	S	↑

Abbreviations: - indicates neutral; ↑, strong recommendation; ↓, weak recommendation; A, usually Appropriate; CRT, chemo-radiation; CT, chemotherapy; EC, expert consensus; EO, expert opinion; fx, fraction; L, limited; M, May be appropriate; M, meta-analysis; M, moderate; MBO, malignant biliary obstruction; NA, not applicable; RT, radiation therapy; S, strong; SMA, superior mesenteric artery; SOE, strength of evidence; SOR, strength of the recommendation; SQ, refers to the study quality (1, 2, 3, or 4) of the references listed; U, Usually not appropriate.

*Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

Variant Discussion:

Dose to Tumor/Tumor bed may depend of final pathology. Preoperative radiation doses are typically 45 – 50 Gy, sometimes with simultaneous integrated boost doses as high as 60 Gy delivered to areas at risk for positive margin using intensity modulated radiation therapy with simultaneous integrated boost technique. Postoperative radiation doses are typically prescribed at 40 – 45 Gy with boost to 50 – 54 Gy for R0 resections and 55 – 59.4 Gy for R1 resections. Hypofractionation may also be considered as preoperative or definitive treatment. Available data most strongly support elective node dose of 40 – 45 Gy but it is not unreasonable to consider doses up to 50.4 Gy to control microscopic disease as the panel feels 40 Gy is somewhat low (expert consensus).

If first echelon lymph nodes are positive consider covering second echelon nodes. Common nodal sites of recurrence for distal ECCs are pancreaticoduodenal, porta hepatis, celiac and SMA.

feasibility of CRT, a high rate of R0 resection (96%), and favorable 3-year OS of 75%.[47] A subsequent retrospective comparison of 106 patients treated with up-front surgery (n = 79) or neoadjuvant CRT (n = 27) showed that neoadjuvant CRT was associated with improved local recurrence (19% vs. 41%), 3-year DFS (78% vs. 58%), and 3-year OS (85% vs. 69%).[46]

Initial series evaluating OLT as curative-intent therapy for unresectable perihilar cholangiocarcinoma were disappointing, with 5-year OS of ~20% to 30% and disease recurrence rates of 50% to 80%.[37,48–50] Thus, 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 before OLT.[51,52] In an early report of 56 patients, 28 underwent OLT (50%). Actuarial 5-year OS was 54% for the entire cohort, but among those who underwent OLT, the 1- and 5-year OS were 88% and 82%.[52] A multi-institutional study from 12 transplant centers, including 287 patients treated with this regimen between 1993 and 2010 demonstrated 2-year and 5-year OS of 68% and 53%, and among those who underwent OLT, 2- and 5-year RFS of 78% and 65%.[37] Favorable outcomes have since been replicated internationally, thus demonstrating the feasibility, broader generalizability, and effectiveness of this treatment strategy.[53–55] 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 before OLT versus OLT alone.[56] Recent series have also shown promising early results with the use of SBRT before OLT for select patients.[57–59]

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 (Table 4).

Adjuvant Therapy

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. 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.[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

TABLE 4. Variant 4: 40 year old male with primary sclerosing cholangitis found to have Clinical Stage I, cT1N0 3 cm hilar cholangiocarcinoma involving the right and left hepatic ducts with extension to the common hepatic duct (Bismuth-Corlette type IV) by MRI. Anatomically unresectable with conventional operation. Child-Pugh score A. Good performance status, tumor meets transplant criteria, and patient is a transplant candidate. (Case for pre-operative CRT + biliary brachytherapy followed by liver transplantation.)

Treatment	Rating category	Group median rating	Disagree	SQ	SOE	SOR
Treatment Options						
Upfront Living Donor Transplant	U	2		-	EC	↑
Neoadjuvant SBRT +/- chemotherapy followed by consideration of OLT	U	3		3,3,3,3	S	↑
Neoadjuvant CT/CRT +/- intraluminal brachytherapy followed by consideration of OLT	M	5		2,2,2,3,3,2,M	S	↑
Definitive CRT	A	8		3,3,3,3	S	↑
RT Alone	M	5		3	S	↑
CT Alone	U	3		1,2,1,2,1	S	↑
CT + immunotherapy	M	4		1,2	S	↑
Targeted Therapy	U	3		2,2,3	S	↑
Best supportive care	U	3		3,2	M	↑
If RT: Dose to Tumor						
40.5-45 Gy/ 30 twice daily fx	A	7		2,2,3,3	S	↑
45 - 60 Gy / 25 -33 fx	A	7		3,2,3,3,3,3,3,3,3,3,2,3,3,3,3	S	↑
45-67.5 Gy/ 15 fx	M	5		3	M	↑
40 -50 Gy/ 5 fx SBRT	M	6		3,3,3,3	S	↑
51-60 Gy/ 5 fx SBRT	U	3		3	M	↑
If RT: Dose to Elective nodes						
40-45 Gy/20-25 fx	A	8		3,2,3,3,3,3,2	S	↑
46-50.4 Gy /23-28 fx	M	5.5		-	EC	↑
40.5-45 Gy/ 30 twice daily fx	A	7		2,2,3,3	S	↑
If RT: Volumes to be included in Clinical Target Volume						
Celiac	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
SMA	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
Porta hepatis (hepatoduodenal ligament and common hepatic)	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
Pancreaticoduodenal	A	7		3,2,3,3,3,3,3,3,2,3	S	↑
Paraaortic	U	3		3,2,3,3,3,3,3,3,2,3	S	↑
GTV or Tumor bed + margin (Adjuvant)	A	9		3,2,3,3,3,3,3,3,2,3	S	↑

Abbreviations: - indicates neutral; ↑, strong recommendation; ↓, weak recommendation; A, usually Appropriate; CRT, chemo-radiation; CT, chemotherapy; EC, expert consensus; EO, expert opinion; fx, fraction; L, limited; M, May be appropriate; M, meta-analysis; M, moderate; MBO, malignant biliary obstruction; NA, not applicable; RT, radiation therapy; S, strong; SMA, superior mesenteric artery; SOE, strength of evidence; SOR, strength of the recommendation; SQ, refers to the study quality (1, 2, 3, or 4) of the references listed; U, Usually not appropriate.

*Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

Variant Discussion:

Aggressive therapy including OLT should be considered in patients with good performance status. For patients who are not candidates for OLT or transplant unavailable, definitive non-surgical options should be considered.

Systemic therapies with or without local therapy or palliative options should be considered for patients with poor performance status

A twice-daily chemoradiation regimen has been specifically evaluated as preoperative therapy prior to OLT. Alternative fractionation schemas can also be considered prior to OLT. Hypofractionated (chemo) radiation may be considered as an alternative to conventional fractionation as definitive therapy for patients who are not candidates for OLT. SBRT may viable treatment option as neoadjuvant or definitive treatment as long as bowel doses are not limiting. In addition, SBRT total dose would be dependent on ability to meet normal tissue tolerances. Elective nodes would not be included in SBRT target volumes.

Available data most strongly support elective node dose of 40 – 45 Gy but it is not unreasonable to consider doses up to 50.4 Gy to control microscopic disease as the panel feels 40 Gy is somewhat low (expert consensus).

Node positivity is an exclusion criteria for consideration of OLT, therefore including second echelon nodes would not typically be indicated (expert consensus). Common nodal sites of recurrence for distal ECCs are pancreaticoduodenal, porta hepatis, celiac, and SMA.

patients with positive surgical margins or positive lymph nodes.[61–66]

Several meta-analyses support adjuvant therapy for the resected disease.[67,68] 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 = 0.67-0.83; $P < 0.001$).[68] A more recent systematic review including 14,646 patients from 22 studies assessing the role of adjuvant therapies in patients with biliary tract cancer (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 to 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).[69]

Approximately 40% of patients with cholangiocarcinoma who do not receive adjuvant RT experience a local or regional failure following surgery.[70] The most common sites of locoregional recurrence after surgery, which should be targeted with adjuvant radiation, include the tumor bed and lymphatics, including hepatoduodenal ligament/hepatic hilum, common hepatic, celiac, pancreaticoduodenal, superior mesenteric, and retroperitoneal nodes.[71–73] Results from a number of retrospective multi-institution and single-institution studies have shown disparate results as to the benefit of adjuvant RT, with

TABLE 5. Variant 5: 68 year old female with clinical Stage I, cT1N0M0 by MRI, hilar cholangiocarcinoma undergoes hepatic resection and regional lymphadenectomy. Final pathology reveals pT1N0 adenocarcinoma (13 nodes retrieved), resected to negative margins. Good performance status.

Treatment	Rating category	Group median rating	Disagree	SQ	SOE	SOR
Treatment Options						
Observation	A	7		3,3,2,3,3	S	↑
Adjuvant CT alone	*M	5	X	M,M,2,1	S	↑
Adjuvant CRT	U	3		3,3,3,3,3,3,3,3,3,3,3,3	S	↑
Adjuvant CT → CRT +/- CT	U	3		2	S	↑
Adjuvant RT alone	U	3		3,3,3,3	S	↑
If RT: Dose to Tumor Bed						
40-45 Gy/20-25 fx	M	5		3,3,3,3,3	S	↑
46-54 Gy /23-30 fx	M	4		3,3,2,3,3,3,3,3,3,2,3,3,3	S	↑
55-60 / 25-33 fx	M	4		3,2,3,3,3,3	S	↑
If RT: Dose to Elective nodes						
40-45 Gy/20-25 fx	A	8		3,2,3,3,3,3,2	S	↑
46-50.4 Gy /23-28 fx	*M	5	X	-	EC	↑
If RT: Volumes to be included in Clinical Target Volume						
Celiac	A	7		3,2,3,3,3,3,3,3,2,3	S	↑
SMA	A	7		3,2,3,3,3,3,3,3,2,3	S	↑
Porta hepatis (hepatoduodenal ligament and common hepatic)	A	7		3,2,3,3,3,3,3,3,2,3	S	↑
Pancreaticoduodenal	A	7		3,2,3,3,3,3,3,3,2,3	S	↑
Paraaortic	U	3		3,2,3,3,3,3,3,3,2,3	S	↑
Tumor bed + margin	A	8		3,2,3,3,3,3,3,3,2,3	S	↑

Abbreviations: - indicates neutral; ↑, strong recommendation; ↓, weak recommendation; A, usually Appropriate; CRT, chemo-radiation; CT, chemotherapy; EC, expert consensus; EO, expert opinion; fx, fraction; L, limited; M, May be appropriate; M, meta-analysis; M, moderate; MBO, malignant biliary obstruction; NA, not applicable; RT, radiation therapy; S, strong; SMA, superior mesenteric artery; SOE, strength of evidence; SOR, strength of the recommendation; SQ, refers to the study quality (1, 2, 3, or 4) of the references listed; U, Usually not appropriate.

*Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

Variant Discussion:

T1N0M0 patients are not well represented in any series, and meta-analysis shows benefit to adjuvant therapy mainly for N+ or + margins

Available data most strongly support elective node dose of 40 – 45 Gy but it is not unreasonable to consider doses up to 50.4 Gy to control microscopic disease as the panel feels 40 Gy is somewhat low (expert consensus).

With adequate node sampling and N0 disease, second echelon nodes in treatment volume would not typically be indicated (expert consensus). Common nodal sites of recurrence for distal ECCs are pancreaticoduodenal, porta hepatis, celiac, and SMA.

some showing a benefit only for patients with node-positive or margin-positive disease.[74–82]

Several single-institution retrospective series have shown that adjuvant CRT improves DFS[83,84] and OS[85] versus observation. While a retrospective NCDB study comparing adjuvant chemotherapy or CRT to surgery alone found that CRT improved OS compared with 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),[86] a systematic review and meta-analysis of 12 studies found no improvement in OS for adjuvant CRT compared with adjuvant chemotherapy alone.[87] The benefit of adjuvant CRT compared with adjuvant chemotherapy or surgery alone may be limited to patients with R1 or R2 resections[88–90]; however, the data is conflicting.[91]

The only multi-institutional, cooperative group prospective, nonrandomized, 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 to 59.4 Gy to the tumor bed).[92] 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.

The role of adjuvant chemotherapy alone 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 2 groups was noted.[93] Negative results were also found for the Phase III PRODIGE 12-ACCORD 18 trial. One hundred ninety-six patients with R0 or R1 resected cholangiocarcinoma were randomized to receive gemcitabine/oxaliplatin versus observation alone. No significant differences in RFS or OS were found.[94] 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. DFS was significantly greater in the capecitabine arm in both the intent-to-treat and per-protocol analysis. Median OS was 51.1 months in the capecitabine 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.[95]

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 (Tables 5 and 6).

TABLE 6. Variant 6: 70 year old female with clinical Stage IIB, cT3NxM0 by MRI, 5 cm hilar cholangiocarcinoma undergoes hepatic resection and regional lymphadenectomy. Pathology confirms a pT3N0 adenocarcinoma (10 nodes retrieved), resected with multiple microscopic positive margins. Good performance status. (Case for positive margins)

Treatment	Rating category	Group median Rating	Disagree	SQ	SOE	SOR
Treatment Options						
Re-excision alone	U	3		-	EC	↑
Adjuvant CT alone	M	6		M,M,2,1	S	↑
Adjuvant CRT	A	7		3,3,3,3,3,3,3,3,3,3,3,3	S	↑
Adjuvant CT → CRT +/- CT	A	7		2	S	↑
Adjuvant RT alone	U	3		3,3,3,3	S	↑
If RT: Dose to Tumor Bed						
40-45 Gy/20-25 fx	*M	5	X	3,3,3,3,3	S	↑
46-54 Gy /23-30 fx	A	7		3,3,2,3,3,3,3,3,3,2,3,3,3	S	↑
55-60 / 25-33 fx	M	5		3,2,3,3,3,3	S	↑
If RT: Dose to Elective nodes						
40-45 Gy/20-25 fx	A	8		3,2,3,3,3,3,2	S	↑
46-50.4 Gy /23-28 fx	M	5		-	EC	↑
If RT: Volumes to be included in Clinical Target Volume						
Celiac	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
SMA	A	7		3,2,3,3,3,3,3,3,2,3	S	↑
Porta hepatis (hepatoduodenal ligament and common hepatic)	A	8		3,2,3,3,3,3,3,3,2,3	S	↑
Pancreaticoduodenal	A	7		3,2,3,3,3,3,3,3,2,3	S	↑
Paraaortic	*M	5	X	3,2,3,3,3,3,3,3,2,3	S	↑
Tumor bed + margin	A	8		3,2,3,3,3,3,3,3,2,3	S	↑

Abbreviations: - indicates neutral; ↑, strong recommendation; ↓, weak recommendation; A, usually Appropriate; CRT, chemo-radiation; CT, chemotherapy; EC, expert consensus; EO, expert opinion; fx, fraction; L, limited; M, May be appropriate; M, meta-analysis; M, moderate; MBO, malignant biliary obstruction; NA, not applicable; RT, radiation therapy; S, strong; SMA, superior mesenteric artery; SOE, strength of evidence; SOR, strength of the recommendation; SQ, refers to the study quality (1, 2, 3, or 4) of the references listed; U, Usually not appropriate.

*Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

Variant Discussion:

The option for re-excision in the setting of positive margins is relatively uncommon. However, in cases where additional surgery is deemed feasible and tolerable, it is the expert consensus of the panel that negative margin status should be achieved if possible, which is typically encountered with focally positive margin. In this case there are multiple positive margins, making it unlikely for re-resection.

Postoperative radiation doses are typically prescribed at 40 – 45 Gy with boost to 50 – 54 Gy for R0 resections and 55 – 59.4 Gy for R1 resections. Available data most strongly support elective node dose of 40 – 45 Gy but it is not unreasonable to consider doses up to 50.4 Gy to control microscopic disease as the panel feels 40 Gy is somewhat low (expert consensus).

With adequate node sampling and N0 disease, second echelon nodes in treatment volume would not typically be indicated (expert consensus). Common nodal sites of recurrence for distal ECCs are pancreaticoduodenal, porta hepatis, celiac, and SMA.

Unresectable EHCC

The prognosis of patients with unresectable EHCC is very poor, and treatment is typically directed at palliation of symptoms related to obstruction.[96] There is a paucity of data to guide the management of these patients and most of the evidence is retrospective. While data suggest that RT 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.[28,97] Existing data suggest that RT delivered with concurrent chemotherapy is superior to both RT and chemotherapy alone for unresectable patients.[98,99] Thus the combination of systemic chemotherapy with RT may be the optimal approach for patients with unresectable disease.

The optimal dose and technique for delivering RT has not been determined.[100,101] A 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% to 36%), and 7% (95% CI: 2% to 20%), respectively, with a median OS of 12 months.[102] 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.[103] A multi-institution retrospective study of dose escalation using protons was found to be effective in 30 patients with unresectable EHCC treated to a median dose of 72.6 Gy.[104]

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 to 48 Gy in 9 to 12 fractions.[105] 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 to 8 cycles of systemic chemotherapy found the 12-month LC rate to be 80% without any observed limiting toxicities.[106]

The pivotal ABC-02 established gemcitabine/cisplatin as the standard first-line treatment for advanced BTC. This phase III study, enrolling 410 patients with locally advanced or metastatic cholangiocarcinoma to receive either cisplatin/gemcitabine versus gemcitabine alone, showed OS was superior in the combination group without the added risk of toxicity.[107] 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.[108]

Other combinations with gemcitabine in the first-line setting have been evaluated.[109–111]

ABC-06 was the first trial to investigate the role of second-line chemotherapy after the progression of disease with platinum-based first line therapy. This randomized phase III study showed a statistical OS benefit for second-line FOLFOX after the progression of gemcitabine plus cisplatin versus best supportive care (OS 6.2 vs. 5.3 mo).[112] Second-line therapies using molecularly targeted agents has also been studied. IDH1/2 mutations are found in 10% to 23% of intrahepatic and 0.8% of EHCCs.[113] A phase III study of 185 patients with advanced IDH1 mutant cholangiocarcinoma treated with the IDH1 inhibitor ivosedenib demonstrated an improvement in PFS (2.7 vs. 1.4 mo; 95% CI = 0·25-0·54; $P < 0.0001$). Mutations in FGFR2 fusions are another potential therapeutic target in advanced BTC. The FIGHT 202 clinical trial, a phase 2 single-arm study, evaluated the safety and efficacy of the FGFR inhibitor pemigatinib in previously treated advanced BTC patients in which 35.5% patients achieved an objective response.[114] Other active targets in cholangiocarcinoma include BRAFV600E mutation, which was shown to be safe and effective in the Phase II ROAR trial.[115] The use of checkpoint inhibition appears to have activity in cholangiocarcinoma tumors that express high tumor mutational burden (TMB-H) or microsatellite instability (MSI-H). Subgroup analysis of the KEYNOTE 158 study investigating the use of the PDL 1 inhibitor pembrolizumab revealed a ORR of 40.9% (95% CI = 20.7%-63.3%), median PFS 4.2 months, OS 24.3 months in patients with cholangiocarinoma.[116]

In summary, the optimal treatment of patients with unresectable EHCC remains to be elucidated (Table 2). Systemic therapy with gemcitabine plus cisplatin is superior to single-agent therapy. CRT may be added in appropriate patients. Molecularly-targeted agents and check-point inhibitors are being studied in the second-line setting.

Radiation Therapy Dose and Technique

In the postoperative setting, any gross residual disease, plus the tumor bed and high-risk elective lymph node regions, should be targeted.[61,76,83,85,89,90,92,117] When delivered preoperatively, the primary tumor plus a margin should be targeted to include elective lymph node regions and microscopic disease extension, which can extend 1.0 to 2.0 cm beyond gross tumor.[118,119] For definitive RT, the gross disease should be targeted, with consideration of elective nodal irradiation, as there are data to suggest the incidence of regional recurrence may be as high as 24% without elective lymph node RT.[120]

For post-operative RT, doses of 40 to 45 Gy in 1.8 to 2.0 Gy fractions should cover the tumor bed, and at-risk elective lymph node regions with an additional tumor bed boost to 50 to 54 Gy is after R0 resection and a 55 to 59.4 Gy after R1 resection.[121–125] In general, intensity modulated RT (IMRT) is the preferred technique.[126] For preoperative RT, doses of 45 to 60 Gy in 1.8 to 2.0 Gy fractions are recommended.[45–47] An alternative regimen, particularly before OLT, is 40.5 to 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 to 25 hours with low dose rate brachytherapy, each prescribed to 1 cm depth.[51,52,54,55] For definitive RT, doses of 45 to 60 Gy in 1.8 to 2.0 Gy fractions have most commonly been used.[101–103,122,120] Hypofractionated regimens of 45 to 67.5 Gy in 15 fractions and 66 to 72 Gy in 10 to 22 fractions have also been used.[104,106] The most commonly reported regimens for SBRT have included 30 to 60 Gy in 3 to 5 fractions.[57–59,120,123,127]

CONCLUSIONS

EHCC is a rare but deadly malignancy. There is a paucity of data regarding the optimal management of these patients, which typically involves multi-modal therapy, including surgery, radiation, and chemotherapy. Owing to this lack of data, all patients should be discussed in a multi-disciplinary setting, and therapy should be tailored to the individual patient's case. Further study is needed to better elucidate the optimal management of these patients.

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