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Upper Gastrointestinal Cancers (L Rajdev, Section Editor)

Multimodality Management of Localized Biliary Cancer

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Opinion statement

Biliary tract cancers (BTCs) are a diverse group of malignancies arising from the biliary tree, including cholangiocarcinoma and gallbladder carcinoma. Patients that are candidates for surgical resection should also have lymphadenectomy. Since recurrence rates are high, after surgical resection, patients should be considered for adjuvant therapy in a multidiscipline setting. The limited availability of randomized clinical trial data makes the optimal treatment option unclear; however, chemotherapy or chemoradiation has been shown to have benefits especially in patients with R1 or R2 resections or lymph node involvement. Patients with unresectable disease should be considered for neoadjuvant therapy with chemotherapy or chemoradiation. Patients that are unable to tolerate chemotherapy should also be considered for locoregional therapies. Clinical trial enrollment is strongly recommended for all patients. Trials involving targeted or immunotherapy are currently ongoing in patients with advanced disease.

Introduction

Biliary tract cancer (BTC) is a heterogenous type of cancer arising from the epithelium of the biliary tree. It is comprised of gallbladder carcinoma (GC) and cholangiocarcinoma (CCA). More than 90% of BTCs are adenocarcinomas [1]. CCAs are classified as intrahepatic (ICCA) or extrahepatic (ECCA). Extrahepatic CCAs are further sub-classified by their anatomical location. Perihilar cholangiocarcinomas (pCCAs) are located at or near the junction of the right and left hepatic ducts. Hilar or Klatskin tumors involve the junction of the right and left hepatic ducts, regardless of origin within the biliary tree. Distal cholangiocarcinomas (dCCAs) occur above the ampulla of Vater and below the confluence of hepatic ducts. Roughly 50% of CCAs are perihilar, 40% are distal, and 10% are intrahepatic [2].

Estimating prevalence of BTCs, particularly CCA, has been challenging due to the differing classification methods of tumors. GC occurs in 1.4 per 100,000 people, with a significantly higher incidence in females [3]. It is more common in non-Hispanic Whites, compared to African Americans. If discovered at the time of localized disease, 5-year survival is roughly 80%. However, unresectable disease has a 5-year survival of < 5% [3, 4]. GC recurrence rates can be as high as 35–60% [5, 6].

ICCA occurs in roughly 0.88 per 100,000 people, and ECCA occurs in 0.72 per 100,0000 [7]. CCAs are more common in males compared to females and more common in Asians and Hispanics [8]. Localized ICCA has a 5-year survival of 10–30%; localized ECCA has a 5-year survival of roughly 10% [4]. Localized BTCs can be cured through complete surgical resection; however, recurrence rates are high. ICCA has a recurrence rate between 46% and 65% [9, 10]. ECCA has recurrence rates of roughly 60% [11, 12].

Risk factors of GC development include cholelithiasis, calcification of the gallbladder (porcelain gallbladder), chronic typhoid infections, primary sclerosing cholangitis, and gallbladder polyps [13]. Prophylactic cholecystectomy may be of benefit for patients with gallbladder polyps > 1 cm or with a porcelain gallbladder. Risk factors for the development of CCA include primary sclerosing cholangitis, hepatolithiasis, choledochal cysts, non-alcoholic fatty liver disease, and hepatobiliary fluke infections by *Clonorchis sinensis* and *Opisthorchis viverinni* [13–17]. Other factors such as HCV, HBV, and cirrhosis have been shown to cause higher incidence of CCA precursor lesions and are a risk factor particularly for ICCA. Diabetes and obesity have also been associated with a higher incidence rate of CCA in some but not all population studies [15]. Lynch syndrome (hereditary non-polyposis colorectal cancer) and multiple biliary papillomatosis are two genetic disorders associated with an increased risk of cholangiocarcinoma.

Staging

Primary tumor staging in GC and ECCA is staged based on tumor invasion into surrounding structures but have gone through changes in classification due to surgical management and clinical outcomes. In American Joint Committee on Cancer (AJCC) eighth edition, T2 GC were divided based on the location of the peritoneal side (T2a) and tumors on the hepatic side (T2b). This revision occurred due to retrospective studies showing that GC located on the hepatic side were associated with worse prognosis, compared to tumors located on the peritoneal side [18, 19]. ECCA were grouped together as a single entity in AJCC sixth edition. The seventh edition of AJCC staging system included a separate TNM classification for perihilar and distal bile duct tumors, to incorporate surgical management. In the revised AJCC eighth edition staging system for cancer of the distal bile duct, depth of tumor invasion has been added to the categorization of T1, T2, and T3 tumors due to studies showing that it had predictive value in patient outcomes. For patients with perihilar ECCA, distal ECCA, and GC, the N category now reflects the number of lymph node (LN) involved. Perihilar ECCA with T4 tumors have also been downstaged to Stage IIIB instead of IV, as these tumors are increasingly considered resectable at tertiary care centers [20–22].

ICCA tumors in AJCC sixth edition were defined by tumor size, similarly to hepatocellular carcinoma. In multiple studies, 5-year overall survival differed based on the presence of multiple tumors, vascular invasion, and lymph node involvement [23, 24]. These findings were then incorporated into AJCC seventh

edition and eighth edition. The revised classification has been validated in predicting survival according to the TNM staging [24].

Determining eligibility for surgical resection

Surgical resection of cholangiocarcinoma depends on the extent of local invasion and the absence of distant metastasis including liver metastasis. Criteria include the absence of retropancreatic and paraceliac nodal metastasis or adjacent organ invasion. Invasion of the main portal vein or main hepatic artery also precludes surgical resection; however, some patients are candidates for resection with vascular reconstruction. pCCAs are likely not surgically resectable if there is involvement of bilateral hepatic arteries, bilateral hepatic duct involvement up to the second order biliary radicals bilaterally, occlusion of the main portal vein proximal to bifurcation, and atrophy of a liver lobe with contralateral vascular involvement.

Anatomical challenges arise in the resection of pCCAs; therefore, staging systems such as the Bismuth-Corlette staging system have been developed to determine surgical approach and feasibility (Fig. 1). This staging system does not include clinicopathologic features such as LN involvement, residual hepatic function, or vascular involvement. Type 1 and type 2 tumors are below or at the confluence of the left and right hepatic artery, respectively, and therefore do not require hepatic resection. Type 3 tumors occlude either left or right hepatic artery. Therefore, hepatic lobectomy is recommended. Type 4 tumors are multicentric or involve the confluence and the hepatic artery. Depending on the tumor location, and surgical expertise, surgical resection may still be possible; however, worse 5-year overall survival has been described [25].

Patients that are eligible for surgical resection should undergo lymphadenectomy. The eighth AJCC staging system recommends for the removal of at least six LN in patients with ICCA and at least four LN in patients with ECCA at the time of surgical resection to adequately determine metastatic involvement [26]. In a recent analysis of National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer database registry from 2000 to 2014 of 1263 patients with ICCA that had surgical resection, it was found that 29% of patients that had nodal evaluation with any number of LN had metastasis. However, only 10% of patients had six or more LN

Fig. 1. Bismuth-Corlette staging system. Type 1, 2, 3a, 3b, and 4 tumors pictured above. Dark green indicates tumor involvement.

Table 1. Randomized control trials impacting the treatment options for adjuvant BTC therapy

Trial name	Type of trial	Tumor type	Intervention	Outcome	*P* value
Edeline et al. (PRODIGE 12-ACCORD 18-UNICANCER GI) [32]	Randomized phase III	Surgically resected (R0 or R1) GC, CCA	Adjuvant GEMOX vs surveillance	RFS = 30.4 months in the GEMOX group vs 18.5 months in the surveillance group, HR = 0.88	$p = 0.48$
				OS = 75.8 months in the GEMOX group vs 50.8 months in the surveillance group, HR = 1.08	$p = 0.74$
Ebata et al. (BCAT) [33]	Randomized phase III	Surgically resected (R0 or R1) pCCA and dCCA	Adjuvant gemcitabine vs surveillance	RFS = 36.0 months in the gemcitabine group vs 39.9 months in the surveillance group, HR = 0.93	$p = 0.69$
				OS = 62.3 months in the gemcitabine group vs 63.8 months in the surveillance group, HR = 1.01	$p = 0.964$
Primrose et al. (BILCAP) [30]	Randomized phase III	Surgically resected GC, CCA	Adjuvant capecitabine vs surveillance	OS = 53 months in capecitabine group and 36 m for observation group	$p = 0.028$
Valle et al. (ABC-02) [31]	Randomized phase III	Locally advanced or metastatic GC, CCA, ampullary cancer	Cisplatin plus gemcitabine compared to gemcitabine	OS = 11.7 vs 8.1 months	$p < 0.001$
Ben-Josef E et al. (SWOG S0809) [32]	Phase II trial	Surgically resected ECCA, GC	Adjuvant capecitabine and gemcitabine followed by concurrent radiation and capecitabine	OS = 35 months	NA

RFS relapse-free survival, *OS* overall survival, *PFS* progression-free survival, *OR* odds ratio, *HR* hazard ratio, *CI* confidence interval, *NA* not applicable

evaluated, and 50% did not have lymphadenectomy [27]. LN metastasis is a strong negative prognostic indicator, with shorter overall survival reported with LN involvement [28, 29].

Role of adjuvant therapy

Cholangiocarcinoma

The optimal adjuvant therapy in localized CCA has not been well established, due to limited randomized data and heterogeneity of patient populations within trials (Table 1). Patients with CCA are recommended adjuvant

Table 2. Meta-analyses and retrospective studies impacting the treatment options for adjuvant BTC therapy

Trial name	Type of trial	Tumor type	Intervention	Outcome	*P* value
Horgan et al. [36]	Meta-analysis	Localized	Adjuvant therapy (chemotherapy, radiotherapy, chemoradiation therapy) vs surgery alone	OR = 0.74	$p = 0.06$
	Meta-analysis	R1 resection	Radiotherapy	OR = 0.33	$p = 0.01$
Zhu et al. [37]	Meta-analysis	Local GC and GC	Fluorouracil vs gemcitabine vs chemoradiation	Fluorouracil HR = 1.61, 95% CI = 0.74–3.67	$p > 0.05$
				Gemcitabine HR = 2.12, 95% CI = 1.23–4.02	$p = 0.01$
				Chemoradiation HR = 1.55, 95% CI = 0.82–3.32	$p > 0.05$
Ma et al. [38]	Meta-analysis	Localized gallbladder cancer	Observation vs fluorouracil- or gemcitabine-based chemotherapy	HR = 0.42, 95% CI = 0.22–0.80	$p < 0.05$
Hyder et al. [39]	Meta-analysis	Localized GC	Radiotherapy vs observation	OS at 1 year = HR 0.45	$p < 0.001$
Kim et al. [40]	Retrospective	Localized ECCA	Chemoradiation vs observation	OS at 5 years = 36.5% vs 28.2%	$p = 0.049$
Tran Cao et al. [41]	Retrospective	Localized GC with LN involvement	Non-operative, surgery alone, adjuvant therapy	OS = 11.6, 13.3, 19.6 months	$p < 0.001$
		Localized ICCA with LN involvement	Non-operative, surgery alone, adjuvant therapy	OS = 12.7, 16.2, 22.6 months	$p < 0.001$

OS overall survival, *PFS* progression-free survival, *OR* odds ratio, *HR* hazard ratio, *CI* confidence interval, *NA* not applicable

chemotherapy or adjuvant chemoradiation, especially if they have had R1 or R2 resection or have LN involvement. Additionally, patients with ICCA and R2 resections can be considered for locoregional therapy.

The optimal adjuvant chemotherapy regimen remains unclear, and clinical trial enrollment is highly recommended. Recommended chemotherapy regimens by consensus guidelines while not on clinical trial are fluoropyrimidine-based or gemcitabine-based. These guidelines were established in part by the BILCAP trial, a phase III randomized clinical trial that included patients with GC and CCA with R0 resections, R1 resections, and LN-positive and negative disease. Patients were randomized to observation or adjuvant capecitabine, and there was an improvement in overall survival (OS) in the per-protocol analysis (HR = 0.75, 95% CI = 0.58–0.97, $p = 0.028$) [30]. This trial was the first and as of

now only phase III trial that showed benefit in adjuvant therapy for BTC.

More recently, the use of gemcitabine-based adjuvant therapy has been called into question by that two phase III clinical trials failed to show benefit in recurrence-free survival (RFS) or OS with adjuvant gemcitabine-based therapies. Prior to these trials, gemcitabine-based adjuvant therapies had been incorporated into consensus-based guidelines based on the ABC-02 trial by Valle et al., which compared gemcitabine to cisplatin and gemcitabine in locally advanced BTC and showed an improved OS of 11.7 months compared to 8.1 months ($p < 0.001$) [31]. However, the randomized phase III trials PRODIGE 12-ACCORD 18-UNICANCER GI (UNICANCER GI) and the Bile Duct Cancer Adjuvant Trial (BCAT) failed to show improvement in RFS or OS with gemcitabine and oxaliplatin (GEMOX) vs surveillance or gemcitabine vs surveillance, respectively. Both trials included patients that had R0 and R1 resections with and without LN involvement. In the UNICANCER GI trial, RFS was 30.4 months in the GEMOX group vs 18.5 months in the surveillance group (HR = 0.88, $p = 0.48$). Median overall survival was 75.8 months in the GEMOX group vs 50.8 months in the surveillance group (HR = 1.08, $p = 0.74$). There was no subgroup with benefit of adjuvant therapy, including those with GC that had statistically worse RFS and OS compared to the surveillance group ($p = 0.034$ for RFS and $p = 0.017$ for OS) [32]. The BCAT had an RFS of 36.0 months in the gemcitabine group vs 39.9 months in the surveillance group (HR = 0.93, $p = 0.69$). The median OS was 62.3 months in the gemcitabine group vs 63.8 months in the surveillance group (HR = 1.01, $p = 0.964$) [33]. These two trials included fewer patients than the BILCAP trial and may have been underpowered. However, their results call into question the use of gemcitabine-based adjuvant therapies.

Chemoradiation was studied prospectively in Southwest Oncology Group (SWOG) S0809, a phase II trial of ECCA and GC patients that received adjuvant capecitabine or gemcitabine followed by concurrent radiation and capecitabine. There were no differences in survival between R0 and R1 resections, median overall survival was 35 months, two-year OS was 65%, and the regimen was generally well tolerated [34]. A subsequent study compared recurrence-free survival and overall survival with adjuvant chemoradiation to surgery alone in patients with R0 resections. Among the patients with LN involvement, patients that received chemoradiation had a longer overall survival (72.1 months, vs 27.2 months, $p = 0.059$). While this trend was not statistically significant, it was absent in the subsets of patients that received chemotherapy or radiation alone as adjuvant therapy compared to surgery alone. This suggests that patients for patients with LN involvement, chemoradiation may be the preferred approach [35]. Such studies justify the use of adjuvant chemotherapy or chemoradiation in patients with R0 resections with positive LN or positive margins, respectively. However, given the heterogeneity of the patient populations within each trial, additional studies are needed, and clinical trial enrollment is recommended.

Adjuvant chemotherapy and chemoradiation for patients with R1 resections, or with LN involvement, have been shown to improve outcomes in a series of meta-analyses and retrospective studies (Table 2). In 2012, a meta-analysis of 22 studies from 1960 to 2010 by Horgan et al. compared 6712 patients with surgically resected BTC that received adjuvant chemotherapy, adjuvant radiotherapy, adjuvant chemoradiation therapy, vs surgery alone. It showed a non-significant improvement in overall survival with any AT

compared with surgery alone (pooled OR 0.74, $p = 0.06$). There was statistically significant improvement in patients with LN-positive disease (OR, 0.49, $p = 0.004$) and R1 resection (OR 0.36, $p = 0.002$). There was greater improvement in survival with chemotherapy, and chemoradiation therapy, compared to radiation alone ($p = 0.02$) [36]. These trials, among others, guide our practice of adjuvant BTC therapy.

In summary, there are few randomized control trials on the role of adjuvant therapy in localized BTC, and those available trials are limited by patient heterogeneity. Consensus-based guidelines for adjuvant therapy by the National Comprehensive Cancer Network (NCCN) are based on the data reviewed. ECCA with negative margins and no LN involvement can be treated with fluoropyrimidine- or gemcitabine-based chemotherapy or observation. Patients with ECCA and positive margins should consider fluoropyrimidine-based chemoradiotherapy followed by fluoropyrimidine- or gemcitabine-based chemotherapy. Patients with ECCA and positive LN involvement should be treated with chemoradiation or fluoropyrimidine- or gemcitabine-based chemotherapy. For patients with ICCA with positive margins, fluoropyrimidine- or gemcitabine-based chemotherapy, fluoropyrimidine- or gemcitabine-based chemoradiotherapy, or locoregional therapy can be considered. Chemoradiotherapy should be considered in all patients with positive margins or LN involvement if possible, as it is preferred over chemotherapy alone in NCCN guidelines [1].

Gallbladder carcinoma

Similar to localized CCA, the role of adjuvant therapy in localized GC requires additional study, as data available is limited by patient heterogeneity and limited randomized control trials (Table 1). Adjuvant chemotherapy or chemoradiation is recommended for all patients with greater to or equal to T2 tumors or positive margins. Chemotherapy with gemcitabine- or fluoropyrimidine-based regimens for 6 months is recommended, in part by findings from BILCAP and ABC [30, 31]. However, as discussed previously, the PRODIGE 12-ACCORD 18-UNICANCER GI and the BCAT trial showed no benefit of adjuvant gemcitabine, and in the PRODIGE 12-ACCORD 18-UNICANCER GI trial, the subset of patients with GC had worse outcomes with adjuvant GEMOX. Chemoradiation with fluoropyrimidine-based regimen and 4 months of systemic gemcitabine and capecitabine remains an alternative, as studied in the phase II SWOG S0809 [34].

Other studies have suggested the utility of adjuvant chemotherapy in localized GC (Table 2). In 2015, a meta-analysis of 10 studies of patients with surgically resected GC found benefit with chemotherapy compared to observation (HR = 0.42, 95% CI = 0.22–0.80). In sub-group analysis, there was OS benefit with adjuvant therapy compared to observation alone for those patients with at least stage II disease, R1 resections (HR = 0.33, 95% CI = 0.19–0.59), or LN involvement (HR = 0.71, 95% CI = 0.63–0.81) [38]. A retrospective study of 1335 patients with GC and 1009 patients with ICCA with LN involvement showed an overall survival benefit of surgery and adjuvant therapy compared to surgery or observation alone [41].

NCCN guidelines recommend patients with negative margins and no LN involvement can be treated with fluoropyrimidine-based chemoradiation, fluoropyrimidine- or gemcitabine-based chemotherapy, or observation. Patients with positive margins or LN involvement are recommended fluoropyrimidine- or gemcitabine-based chemotherapy or fluoropyrimidine- vs gemcitabine-based chemoradiotherapy followed by fluoropyrimidine- or gemcitabine-based chemotherapy. Since the optimal adjuvant therapy has yet to be elucidated, clinical trial is strongly recommended [1].

Role of neoadjuvant therapy

It has been well-established that the patients with locally advanced biliary tract cancer who are treated with chemotherapy alone have a poor prognosis. Therefore, there have been several studies that have examined the role of neoadjuvant therapy and effectively downsizing the tumor in order to then pursue curative surgery. Preoperative (neoadjuvant) chemoradiotherapy cannot be considered a standard approach to treatment of cholangiocarcinoma. Rarely, patients with large, locally advanced unresectable cholangiocarcinoma who are treated with chemoradiotherapy are converted to potentially resectable disease, and resection could be considered in this setting.

ICCA and ECCA when possible should be managed with either chemotherapy, chemoradiation, or locoregional therapies for downsizing. Chemotherapy regimens are based on studies of the treatment of advanced and surgically resected CCA (Table 1). The primary chemotherapy regimen recommended for neoadjuvant therapy is gemcitabine and cisplatin, based on the ABC trial, or a fluoropyrimidine-based regimen, based on the BILCAP trial, or other gemcitabine-based regimens based on trials in pancreatic cancer [30, 31]. Given the lack of a standard neoadjuvant therapy regimen, clinical trial enrollment is highly recommended for all patients receiving neoadjuvant therapy.

In select patients, liver transplantation can be considered. Orthotopic liver transplantation (OLT) might be considered for highly selected patients with early stage cholangiocarcinoma arising in the setting of primary sclerosing cholangitis (PSC) or for those with early stage, small, but unresectable hilar cholangiocarcinomas who have successfully completed rigorous staging and neoadjuvant therapy. OLT should only be carried out after careful consideration at experienced centers, preferably within the context of a clinical trial.

Intrahepatic CCA

Patients with unresectable disease should be treated with chemotherapy, locoregional therapy, or a clinical trial. Chemotherapy regimens of choice were discussed above. The feasibility of neoadjuvant chemotherapy was investigated by Le Roy et al. in the treatment of unresectable ICCA. In a retrospective study with 186 patients, 39 patients with locally advanced disease were treated for a median of six chemotherapy cycles prior to surgery. There was no statistically significant difference ($p = 0.391$) in median survival between the 82 patients treated with upfront surgery (25.7 months) vs the 39 patients with locally advanced disease who were treated with neoadjuvant chemotherapy followed by surgery (24.1 months). In addition, for the patients with locally advanced

cancer, those treated with neoadjuvant chemotherapy and surgery had a median overall survival of 3 years vs 11 months if treated with chemotherapy alone. Although retrospective in nature, this study suggests that neoadjuvant chemotherapy is an effective treatment option in the management of locally advanced ICCA [42].

Although ICCA has been considered a contraindication for liver transplant, a recent prospective case-series by Lunsford et al. examined the use of neoadjuvant chemotherapy followed by liver transplantation in 12 patients, 6 of whom underwent liver transplant. After receiving treatment, the patients were required to have stable or regressed disease prior to receiving liver transplant. The overall survival of the patients was 100% at 1 year, 83.3% at 3 years, and 83.3% at 5 years. This study demonstrates a potential benefit for neoadjuvant chemotherapy and liver transplantation in the intrahepatic cholangiocarcinoma population [43]. More data on the use of liver transplantation in the treatment of ICCA is needed, and patients receiving transplant should do so though clinical trial when possible.

Extrahepatic cholangiocarcinoma

Patients with unresectable ECCA should be considered for chemotherapy. Optimal regimens remain gemcitabine and cisplatin, gemcitabine-based regimen, or a fluoropyrimidine-based chemotherapy or chemoradiotherapy [30, 31, 34]. Patients should also be considered for transplant, which has been established as a treatment option for Klatskin tumors. Unresectable patients with Klatskin tumors can be managed with a combination of neoadjuvant chemoradiation and liver transplantation. The Mayo Clinic developed a protocol in 2005 in which patients with Klatskin tumors were treated with neoadjuvant chemoradiation followed by liver transplant vs resection. In the 38 patients treated with liver transplant, there was a better 5-year survival rate (82%) compared to the patients with liver resection (21%). In addition, there were lower rates of recurrence in the liver transplant group (13% vs 27%). Unfortunately, the two treatment groups were not comparable with respect to age, LN status, and metastases [44].

More recently, Loveday et al. did a prospective study in the Klatskin tumor population using the combination of neoadjuvant chemoradiation and liver transplantation. Ultimately, 6 of the 43 screened patients underwent liver transplantation. The protocol included chemoradiation with capecitabine, surgical staging, maintenance chemotherapy with gemcitabine and cisplatin, and liver transplant for eligible patients. For the transplanted population, the 1- and 2-year post-transplant survival was 83.3% and 55.6%, which has been lower than the survival rate reported in other studies [45]. This was a very small patient population, however, and the survival rates could easily be influenced by outlier patients. Long-term survival data is not yet available. On the other hand, Darwish Murad et al. looked at the use of neoadjuvant chemoradiation followed by liver transplant in 214 patients at 12 US centers and found a 65% rate of recurrence-free survival after 5 years and overall survival of 68% at 2 years [46]. In the future, it will be important to elucidate the reason for different outcomes between centers with a neoadjuvant chemoradiation and liver transplantation treatment plan for Klatskin tumors.

Gallbladder carcinoma

There are limited studies on neoadjuvant therapy for GC; therefore, clinical trial enrollment is highly recommended. If patients are treated off protocol, chemotherapy and chemoradiotherapy regimens discussed for CCA are recommended for GC. Non-randomized studies have evaluated the clinical utility of neoadjuvant chemotherapy. A retrospective study by Sirohi et al. looked at the use of neoadjuvant chemotherapy with gemcitabine- and platinum-based chemotherapy in the treatment of 37 patients with locally advanced gallbladder cancer. In this study, 17 of the patients were able to achieve an R0 resection with the remainder having progressed or remaining unresectable. The patients who received the neoadjuvant chemotherapy and underwent surgery had a significantly better overall survival (median not reached vs 9.5 months with $p = 0.001$) and progression-free survival (25.8 vs 5.6 months with $p < 0.0001$) compared to those who did not receive surgery. Although this was another retrospective study, it again established the role of neoadjuvant chemotherapy in gallbladder cancer [47].

A prospective study by Engineer et al. looked at the use of neoadjuvant chemoradiation followed by surgery in the treatment of patients with locally advanced gallbladder cancer. Of the 28 patients treated with chemoradiation involving gemcitabine, 14 patients underwent surgery with an R0 resection. The median 5-year overall survival rate for the patients who underwent the R0 resection was 35 vs 10 months for the other patients. However, those excluded from surgery were mostly excluded due to known established progression after receiving the neoadjuvant chemoradiation. This study still suggests a potential more aggressive treatment option in otherwise unresectable and incurable locally advanced gallbladder cancer [48].

Locoregional therapies

There are additional locoregional therapies that can be used in the treatment of unresectable intrahepatic cholangiocarcinoma. Percutaneous radiofrequency ablation (RFA) is an effective approach regardless of tumor vascularity and is most effective in patients with smaller tumors [49]. Radiofrequency ablation is also used as a treatment for malignant biliary occlusion in conjunction with stent placement for unresectable hilar cholangiocarcinoma patients [50]. In a recent article by Zhang et al., there was a statistically significant improvement in overall survival of the patients who underwent RFA with stenting vs stenting alone (13.2 vs 8.3; $p < 0.001$). The patency of the stents was significantly improved as well [51]. This suggests an effective and safe approach to stenting in extrahepatic cholangiocarcinoma patients. Other ablative techniques include cryoablation and percutaneous alcohol injection, but they are less commonly used.

Chemoembolization is an additional locoregional approach for patients with unresectable intrahepatic cholangiocarcinoma. The use of transarterial chemoembolization (TACE) with drug-eluting beads (DEB) was validated by Kulhmann et al. as the median overall survival of this group was 11.7 months compared to conventional TACE in which it was 5.7 months [52]. In a study by Aliberti et al., TACE was used with DEB loaded with doxorubicin or polyethylene glycol drug-elutable microspheres (PEG) in 127 patients. Seventy-seven percent of patients treated with PEG achieved a partial response compared to 7% of those treated with DEB. The majority of the patients treated with DEB had stable disease

[53]. This suggests a safe and effective treatment option for locoregional control of unresectable intrahepatic cholangiocarcinoma. Zhao et al. studied the efficacy and safety of TACE with gemcitabine and oxaliplatin in 65 patients with unresectable advanced biliary tract cancer. Of the treated patients, 19 (29.2%) achieved a partial response, 36 (55.4%) showed stable disease, and 10 (15.4%) showed progressive disease [54]. This again confirms the safety and efficacy of TACE.

Yttrium-90 radioembolization is another arterial-directed locoregional therapy for treating unresectable intrahepatic cholangiocarcinoma. The isotope is injected through catheters in the hepatic artery. The catheters then release radiation to tumor cells with minimal damage to normal liver tissue. Normal tissue uses the portal vein for its blood supply while tumor tissue uses the hepatic artery [55]. Hoffmann et al. did a retrospective study of 33 intrahepatic cholangiocarcinoma patients treated with Yttrium-90 and found an overall response rate of 36.3% (12 with a partial response) and a median overall survival of 22 months [56]. Additional studies have shown that Yttrium-90 is a safe and effective option [57, 58]. Yttrium-90 was also recently effectively used as a downstaging option for eight initially unresectable intrahepatic cholangiocarcinoma patients in conjunction with neoadjuvant chemotherapy prior to resection [59].

In summary, locoregional therapies should be considered a therapeutic option for patients with unresectable disease or in patients who are unable to tolerate chemotherapy. Ablative techniques such as RFA and cryo-ablation are effective in smaller tumors. Arterial-directed therapies such as TACE or Yttrium-90 can be used in larger tumors, but an elevated bilirubin of > 3 mg/dl is a relative contraindication to this treatment.

Future directions

There is an emerging role for precision medicine in the management of cholangiocarcinoma. As of now, there is no effective targeted therapy for advanced cholangiocarcinoma. However, clinical trials investigating potential targets are ongoing for patients with advanced disease. About 11–14% of ICCA have FGRF2 fusion genes. This mutation is associated with a favorable prognosis, younger age at onset, and female predilection [60]. Several FGFR kinase inhibitors, such as INCB054828 (NCT02924376), are being evaluated in clinical trials in patients with surgically unresectable disease. Isocitrate dehydrogenase 1 and 2 (IDH1/2) mutations are found in 7–36% of ICCA [61]. There is an ongoing phase III trial (NCT02989857) investigating the use of IDH1 inhibitors in the treatment of advanced ICCA. HER2 amplification has also been found in 5–25% of extrahepatic bile duct carcinomas and 16–17% of gallbladder carcinomas and is typically associated with poor prognosis. A retrospective study by Javle et al. used HER2 blockade in nine patients with gallbladder carcinomas who had HER2 amplification with the patients experiencing stable disease, partial response, or complete response. On the other hand, they did the same with cholangiocarcinoma patients and found no response [62].

Given the efficacy of immune checkpoint inhibitors in the treatment of various malignancies, the expression of programmed cell death protein ligand-1 (PD-L1) was examined in biliary tract cancer. Its expression is significantly higher in biliary tract cancer categorized as poor prognosis from a genomic perspective [63]. Therefore, there are several clinical trials investigating

the use of anti-PD-1 antibodies in the treatment of advanced biliary tract cancer including KEYNOTE-028. There are additional clinical trials combining chemotherapy with immunotherapy. Therefore, in the absence of standard treatment options for unresectable tumors, molecular testing and enrollment in clinical trials with targeted or immunotherapy can be considered as their roles in advanced disease become clarified.

Summary

In conclusion, patients with localized GC or CCA can be cured through surgical resection, but recurrence rates can be as high as 65%. Patients are recommended adjuvant chemotherapy or adjuvant chemoradiation, particularly if they have had R1 or R2 resection or have LN involvement. Additionally, patients with ICCA and R2 resections can be considered for locoregional therapy. Neoadjuvant chemotherapy or chemoradiation remains an option for patients with unresectable disease. Optimal regimens for adjuvant and neoadjuvant therapy remain unclear due to lack of randomized trials, and patient heterogeneity within trials. Therefore, clinical trial enrollment is strongly recommended. Patients with ICCA or Klatskin tumors that are unresectable can also be considered for liver transplantation. Locoregional therapies, including RFA, chemoembolization, and radioembolization, are also options for patients with unresectable disease or patients that cannot tolerate chemotherapy. Emerging therapies that are being studied in patients with advanced disease include the use of immunotherapy and targeted therapy. It remains unclear how targeted therapies and immunotherapy will be incorporated into localized disease management and remains an area of future investigation.

Compliance with Ethical Standards

Conflict of Interest
Nadia Ashai, Preethi Prasad, and Lakshmi Rajdev declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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