Review

Systemic and Adjuvant Therapies for Intrahepatic Cholangiocarcinoma

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Yun Shin Chun, MD[1], and Milind Javle, MD[2]

Abstract

Intrahepatic cholangiocarcinoma represents the second most common primary liver cancer and is increasing in incidence. Most patients are diagnosed at an advanced, nonsurgical stage and only about 1 in 5 cases are surgically resectable. Despite surgery, the 5-year survival is low at only 30%. Multifocal, node- or margin-positive disease is at a higher risk of recurrence after resection. There is no level 1 evidence in support of postoperative adjuvant therapy. A recent adjuvant therapy phase III trial from the Partenariat de Recherche en Oncologie Digestive-Actions Concertées dans les Cancers Colo-Rectaux et Digestifs (PRODIGE) group reported no survival advantage with adjuvant gemcitabine and oxaliplatin therapy. Locally advanced or metastatic cholangiocarcinoma is treated with gemcitabine-based systemic chemotherapy with suboptimal response and survival. Integration of local therapy such as focal radiation along with induction chemotherapy is now being investigated in multicenter clinical trials. Recent molecular profiling studies have indicated that about 30% to 40% of intrahepatic cholangiocarcinoma cases have actionable mutations. These include fibroblast growth factor receptor (FGFR), isocitrate dehyrogenase 1 (IDH1), epidermal growth factor receptor (EGFR), and BRAF genetic aberrations. Clinical trials targeting these mutations as well as immune therapy using programmed cell death 1 (PD1) inhibitors indicated a promising early signal showing clinical efficacy.

Keywords

intrahepatic cholangiocarcinoma

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Introduction

In the United States, an estimated 3000 intrahepatic cholangiocarcinomas are diagnosed annually.[1] Overall, the incidence of this disease is increasing worldwide. Part of the reason for this increase is that adenocarcinomas of unknown primary are now being reclassified as intrahepatic cholangiocarcinoma. However, this cannot be the only explanation as Klatskin tumors, previously classified as intrahepatic, are now being classified as extrahepatic cholangiocarcinoma.[2] The increased incidence of obesity and associated nonalcoholic fatty liver disease and nonalcoholic steatohepatitis may account for the increased incidence of primary liver cancer including cholangiocarcinoma, particularly in the Western world.[3,4] Presenting symptoms are nonspecific and include abdominal discomfort, weight loss, indigestion, or asymptomatic elevation of liver functions on routine laboratory testing. A minority of patients are diagnosed at a surgically resectable stage, and the recurrence rate following surgery is 60% to 70%. Therefore, postoperative adjuvant therapy is often considered and is discussed below.

Adjuvant Therapy

Surgical resection is the only potentially curative treatment for intrahepatic cholangiocarcinoma and is associated with 5-year overall survival rates between 15% and 40%.[5]

[1] Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA
[2] Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Corresponding Author:
Milind Javle, Department of Gastrointestinal Medical Oncology, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
Email: mjavle@mdanderson.org

However, up to two-thirds of patients have postoperative disease recurrence, most commonly in the remnant liver.[6] Other common sites of recurrence include the peritoneum and abdominal lymph nodes.[7] Prognostic factors associated with disease recurrence are vascular invasion, multiple tumors, and lymph node metastases. There is a paucity of data on adjuvant therapy due to the small numbers of patients undergoing resection of intrahepatic cholangiocarcinoma and lack of response to traditional systemic chemotherapy. Moreover, several studies are difficult to interpret due to the inclusion of patients with extrahepatic bile duct and gallbladder cancer and, in some cases, ampullary cancer.

Studies Focused on Intrahepatic Cholangiocarcinoma

To date, all the published studies focused on adjuvant treatment of intrahepatic cholangiocarcinoma are retrospective (Table 1). Jiang et al[8] examined the role of adjuvant external beam radiation therapy for patients with residual lymph node metastases. Arguably, the presence of gross residual disease after resection implies that radiation was delivered as primary or palliative treatment and not adjuvant. The radiotherapy (n = 24) and nonradiotherapy (n = 66) groups had statistically similar rates of multicentric disease and tumor size >5 cm. The decision to treat with radiation was at the discretion of the treating physicians. The median overall survival of the radiotherapy group was 19.1 months (95% confidence interval [CI]: 11.5-26.7 months) compared to 9.5 months (95% CI: 4.4-14.7 months) in the nonradiotherapy group ($P = .011$). In the radiotherapy group, the most common causes of death were intrahepatic recurrence in 31% of patients and distant metastases in 31% of patients. In the nonradiotherapy group, intrahepatic recurrence accounted for 59% of deaths. Lymph node metastases were identified as the cause of death in a minority of patients. In view of the high incidence of disease failure outside the radiation field and small numbers of patients, the results of this study do not support the use of radiation alone as adjuvant treatment.

Two studies from China examined the efficacy of adjuvant transarterial chemoembolization (TACE) after resection of intrahepatic cholangiocarcinoma. In both studies, TACE was performed by injecting iodized oil with 5-fluorouracil, epirubicin, and hydroxycamptothecin. In a series from Fudan University, patients undergoing R0 resection were analyzed separately from those undergoing R1/2 resections and palliative procedures.[9] Among those undergoing R0 resection, 68 patients received postoperative TACE and 143 patients no TACE. On multivariate analysis of factors related to overall survival, absence of adjuvant TACE was associated with significantly worse overall survival (hazard ratio [HR]: 1.77; 95% CI: 1.15-2.73; $P = .010$). Paradoxically, absence of adjuvant TACE was associated with lower risk of disease recurrence (HR: 0.59; 95% CI: 0.38-0.92; $P = .020$). When stratified by stage, approximately half the patients undergoing R0 resection had stage I disease, for which adjuvant TACE was associated with higher disease recurrence: 51% with TACE versus 24% no TACE ($P = .006$). The authors hypothesize that TACE-induced hypoxia can induce local angiogenic factors that promote tumor metastasis, particularly among stage I patients.

Another series from Eastern Hepatobiliary Surgery Hospital in Shanghai analyzed 122 patients who received adjuvant TACE and 431 patients who underwent R0 resection alone.[10] Five-year recurrence rates were significantly lower with adjuvant TACE: 73% and 78% with and without adjuvant TACE, respectively ($P = .039$). Similarly, adjuvant TACE was associated with improved overall survival, with 5-year overall survival rates of 38% and 30% with and without TACE ($P = .007$), respectively. However, after 1:1 propensity score matching, adjuvant TACE was not associated with higher overall or recurrence-free survival. The entire patient cohort was stratified into tertiles by an intrahepatic cholangiocarcinoma nomogram based on factors such as tumor size, number, and vascular invasion. Patients in the lowest tertile with the worst prognostic features had 5-year overall survival rates of 21.3% and 6.2% with and without TACE ($P = .001$), respectively. Based on this study and the series from Fudan, adjuvant TACE may be considered for patients with poor prognostic factors, particularly in the context of a clinical trial.

In a report by Ercolani et al,[11] adjuvant gemcitabine-based chemotherapy was administered to 25 (35%) of 72 patients undergoing resection of intrahepatic cholangiocarcinoma. Isolated intrahepatic recurrence accounted for 64% of disease recurrences. Five-year overall survival rates with and without chemotherapy were 65% and 40%, respectively ($P < .05$), but the favorable prognostic effect of adjuvant chemotherapy was lost on multivariate analysis.

Database Studies

Two studies from the United States evaluated the results of adjuvant therapy for intrahepatic cholangiocarcinoma using the National Cancer Data Base (NCDB). Both studies are limited by missing data, including important clinicopathologic variables such as vascular invasion and number of tumors. Sur et al searched the NCDB from 1998 to 2006 and identified 75 patients treated with adjuvant chemotherapy, 147 with chemoradiation, and 416 with no adjuvant therapy.[12] Patients receiving adjuvant therapy were more likely to have lymph node metastases (31% adjuvant therapy vs 14% no adjuvant therapy; $P < .001$) and positive resection margins (46% adjuvant therapy vs 18% no adjuvant therapy; $P < .001$). On multivariate analysis, there was a statistically significant survival benefit with both chemotherapy (HR: 0.73; 95% CI: 0.54-0.98) and chemoradiation (HR: 0.77; 95% CI: 0.61-0.99). After adjusting for other prognostic factors, the improvement in survival with adjuvant therapy was restricted to patients with positive lymph nodes and/or resection margins.

Miura et al[13] searched the NCDB between 1998 and 2011 and compared 985 patients who received chemotherapy to a propensity-matched cohort of patients who did not receive chemotherapy. Chemotherapy was administered as adjuvant treatment in 55% of patients, neoadjuvant in 10%, and unknown

Table 1. Studies on Adjuvant Therapy for Intrahepatic Cholangiocarcinoma.[a]

Author, Year	No. of Patients	Major Hepatectomy	Lymph Node Metastases	Tumor Size > 5 cm	Multiple Tumors	Vascular Invasion	Positive Margin	Recurrence	Overall Survival
Jiang et al [8]	90 total: 24 pts EBRT vs 66 no EBRT	NA	100%	61 (68%)	14 (16%)	NA	NA	Intrahepatic: [b] 5 (31%) EBRT vs 32 (59%) no EBRT	Median 19.1 months EBRT vs 9.5 months no EBRT ($P = .011$)
Li et al [9]	211 total: 68 TACE vs 143 no TACE	NA	34 (16%)	139 (66%)	38 (18%)	50 (24%)	0	81 (38%) total. Stage I: 18/35 (51%) TACE vs 15/63 (24%) no TACE, $P = 0.006$.	No TACE: HR for death: 1.77; 95% CI: 1.15-2.73; $P = .010$
Li et al [10]	553 total: 122 TACE vs 431 no TACE	104 (19%)	13 (11%) TACE vs 91 (21%) no TACE	Median: 5.5 cm TACE vs 6 cm no TACE	25 (21%) TACE vs 132 (30%) no TACE	73 (13%)	0	5-year 73% TACE vs 78% no TACE ($P = 0.039$)[c]	5-year 38% TACE vs 30% no TACE ($P = .007$)[b]
Ercolani et al [11]	72 total: 25 gemcitabine-based CTX vs 47 no CTX	46 (64%)	12/41 (29%)	40 (56%)	9 (13%)	24 (33%)	12 (17%)	39 (54%)	5-year 65% CTX vs 40% no CTX ($P < .05$)[d]
Sur et al [12]	638 total: 75 EBRT, 147 CRT, 416 no treatment	327 (51%)	21 (28%) CTX vs 48 (33%) CRT vs 59 (14%) no treatment	40 (53%) CTX vs 37 (25%) CRT vs 153 (37%) no treatment	NA	NA	27 (36%) CTX vs 76 (52%) CRT vs 76 (18%) no treatment	NA	Benefit with CTX: HR: 0.54 positive nodes, HR: 0.44 positive margins. Benefit with CRT: HR: 0.5 positive nodes, HR: 0.57 positive margins
Miura et al	1970 total: 985 CTX vs 985 no. CTX[e]	821 (42%)	430 (22%)	820 (42%)	NA	NA	639 (32%)[f]	NA	Median 23 months CTX vs 20 months no CTX ($P = .09$).

Abbreviations: CI, confidence interval; CTX, chemotherapy; CRT, chemoradiation; EBRT, external beam radiation therapy; HR, hazard ratio; NA, not available; TACE, transarterial chemoembolization.
[a]n (%).
[b]Death from intrahepatic recurrence.
[c]After propensity score matching, there was no difference in 5-year recurrence or overall survival with TACE.
[d]Not significant on multivariate analysis.
[e]Propensity score–matched cohorts.
[f]Unknown margin status in 14% of patients.

sequence in 35% of patients. In the chemotherapy group, only 53% of patients underwent R0 resection. Similar to the study by Sur et al, a benefit with adjuvant chemotherapy was observed among patients with nodal metastases and positive margins. For both NCDB studies, the high rate of positive resection margins calls into question the indications and therapeutic benefit of surgery in these patients.

The Surveillance, Epidemiology, and End Results (SEER) registry was analyzed for the impact of adjuvant radiation on the overall survival after resection of intrahepatic cholangiocarcinoma.[14] Among 3839 patients, 948 (25%) underwent surgery alone and 286 (7%) received adjuvant radiation. Most patients in the database received no treatment. Median overall survival with adjuvant radiation was 11 months compared to 6 months with surgery alone ($P = .014$). The authors performed propensity score–adjusted analysis, controlling for age, race, stage of the disease, and year of diagnosis, and confirmed an improvement in the overall survival with adjuvant radiation over surgery alone (HR: 0.82; 95% CI: 0.70-0.96). However, data on important prognostic factors, including the extent of surgery and margin status, were missing. Furthermore, cancer stage was classified as distant, localized, or regional. Therefore, a benefit with adjuvant radiation cannot be determined from this SEER analysis.

Studies Including Other Biliary Tract Cancers

Two randomized controlled trials have been conducted on adjuvant chemotherapy after resection of biliary tract cancers. Takada et al randomized a total of 436 evaluable patients, including 118 with bile duct cancer, to postoperative chemotherapy with 5-fluorouracil and mitomycin C or surgery alone.[15] Only patients with gallbladder cancer (n = 112) were found to have a significant improvement in the overall survival with adjuvant chemotherapy. The second randomized trial, the European Study Group for Pancreatic Cancer (ESPAC)-3, included 96 patients with bile duct cancer who were randomized to adjuvant chemotherapy with 5-fluorouracil (n = 31) or gemcitabine (n = 34), or observation (n = 31).[16] After adjusting for independent prognostic factors, adjuvant chemotherapy was associated with significantly higher survival (HR: 0.75; 95% CI: 0.57-0.98; $P = .03$) among all patients analyzed in ESPAC-3, including 69% who had ampullary cancers. Neither the study by Takada nor ESPAC-3 specifies the location of the bile duct cancer, and therefore, conclusions about the efficacy of adjuvant chemotherapy in intrahepatic cholangiocarcinoma cannot be drawn.

Horgan et al performed a systemic review and meta-analysis on adjuvant therapy for biliary tract cancers, evaluating 6712 patients from 20 studies published between 1960 and 2010.[17] The authors found a nonsignificant improvement with adjuvant therapy compared with surgery alone (odds ratio [OR]: 0.74; $P = .06$). After exclusion of 2 SEER analyses, there was a significant benefit with adjuvant therapy, particularly with chemotherapy (OR: 0.39) or chemoradiation (OR: 0.61) over radiation alone (OR: 0.98). Patients with lymph node metastases (OR: 0.49) and R1 disease (OR: 0.36) derived the greatest benefit from adjuvant therapy. However, only 1 study included patients with intrahepatic cholangiocarcinoma (n = 11). Thus, the results of this meta-analysis cannot be applied to patients with intrahepatic cholangiocarcinoma.

Ongoing Trials

Given the rising incidence and mortality from intrahepatic cholangiocarcinoma, disease-specific prospective studies are needed. ACTICCA-1 is a randomized phase III trial accruing patients in Europe and Australia to adjuvant gemcitabine and cisplatin compared to observation after resection of cholangiocarcinoma and gallbladder cancer (NCT02170090).[18] Patients are stratified by lymph node status and location of cholangiocarcinoma. In Shanghai Zhongshan Hospital, patients with intrahepatic cholangiocarcinoma are being accrued to a phase III study of adjuvant gemcitabine and oxaliplatin versus capecitabine (NCT02548195). Two phase 3 studies of bile duct cancer, including intrahepatic cholangiocarcinoma, have completed accrual. The BILCAP study from the United Kingdom randomized patients to adjuvant capecitabine or observation (NCT00363584). Results from this trial are eagerly awaited. PRODIGE-12 from France randomized patients to adjuvant gemcitabine and oxaliplatin or observation (NCT01313377). This study was presented at the Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology in 2017. This study randomized 190 patients to gemcitabine and oxaliplatin chemotherapy versus surveillance alone and reported no significant improvement in survival with adjuvant therapy. Eighty-six intrahepatic cholangiocarcinoma cases were randomized in this trial. Unfortunately, there was no preselection for high-risk cases in this study. About 50% of those enrolled had multifocal tumor, and one-third had node-positive disease. Inclusion of cases with a lower risk of recurrence may have obfuscated the results. At the present time, unless the BILCAP trial suggests otherwise, there is no rationale for the routine use of adjuvant therapy in resected intrahepatic cholangiocarcinoma. Patients at high risk should be offered enrollment in prospective clinical trials. For the vast majority of intrahepatic cholangiocarcinomas though, resection or local ablation is not feasible, and systemic therapy remains the only option.

Systemic Therapy

Systemic chemotherapy for biliary tract cancers has traditionally followed the regimens used for advanced pancreatic cancers including single-agent gemcitabine, gemcitabine with capecitabine, and gemcitabine with platinum analogues, including cisplatin, oxaliplatin, and carboplatin. It has been almost 10 years since the publication of Advanced Biliary Tract (ABC)-02 phase III trial of gemcitabine and cisplatin versus gemcitabine as a single agent.[19] This study followed a randomized phase II trial that suggested superiority of the doublet as compared with gemcitabine alone. This phase III trial randomized 410 patients from the United Kingdom and

Table 2. Most Frequently Seen Mutations in Intrahepatic Cholangiocarcinoma.

Reference	ICGC 2015[33]	Zou et al [34]	Javle et al [35]	Jiao et al[28]	Simbolo et al[36]	TCGA	IHCCA Total
Country	Japan	China	United States	United States	Italy	United States /Canada	
N	135	102	412	64	70	32	815
TP53	22%	38%	27%	6%	9%	6%	21%
KRAS/NRAS	27%	18%	22%	11%	23%	3%	20%
IDH1/2	10%	5%	20%	20%	20%	19%	14%
ARID1A	17%	7%	12%	14%	11%	16%	14%
BAP1	10%	1%	15%	20%	14%	38%	12%
PBRM1	9%	1%	7%	13%	14%	25%	9%
***FGFR2* fusion**	4%	ND	11%	ND	ND	16%	6%
PIK3CA	9%	3%	5%	3%	6%	6%	6%
PTEN	0%	7%	5%	3%	1%	3%	3%
***BRAF* hotspot**	0%	1%	5%	0%	4%	3%	2%
***ARAF* hotspot**	0%	1%	ND	3%	ND	6%	1%
RB1	1%	5%	0%	0%	0%	0%	1%

Abbreviation: ND, not determined.

reported a significant improvement in overall survival with gemcitabine and cisplatin as compared with gemcitabine alone (11.7 months vs 8.1 months; HR: 0.64; $P < .001$). In all, 80 patients with intrahepatic cholangiocarcinoma were included in the study and they experienced a significant improvement in survival with the doublet (HR: 0.57). However, patients with Eastern Cooperative Oncology Group performance status of 2 experienced no improvement in survival with the gemcitabine + cisplatin, and in clinical practice, these patients should be offered monotherapy.

Unlike the improvement in survival achieved in colorectal and gastric cancers with a combination of cytotoxic chemotherapy with biologic agents, higher survival in intrahepatic cholangiocarcinoma has not been demonstrated with the addition of a biologic agent to the gemcitabine–platinum backbone. The ABC-03 trial was a multicenter, double-blind, placebo-controlled phase 2 trial that randomly assigned 124 patients to cediranib, an oral vascular endothelial growth factor inhibitor, or placebo, in combination with gemcitabine and cisplatin.[20] Progression-free survival was 8.0 and 7.4 months, with and without cediranib ($P = .72$). Anti–EGFR therapy also did not impact survival in the phase 2 randomized BINGO trial, gemcitabine and oxaliplatin with or without cetuximab.[21] In this multicenter trial of 150 patients from France and Germany, the addition of cetuximab to gemcitabine and oxaliplatin did not lead to improved progression-free or overall survival (with and without cetuximab: progression-free survival, 6.1 vs 5.5 months; overall survival, 11.0 vs 12.4 months).

Intrahepatic cholangiocarcinoma, in particular T2 tumors that are not surgically resectable, maybe considered for local ablation with radiotherapy.[22,23] The appropriate sequencing of chemotherapy with radiation in this situation has not yet been established. The NRG-GI001 trial is evaluating induction chemotherapy with gemcitabine and cisplatin followed by radiotherapy or observation. This is also the scheme for the ongoing ABC-08 trial that randomizes patients to chemotherapy alone or followed by stereotactic body radiotherapy.

Second-line chemotherapy options for cholangiocarcinoma have included gemcitabine or fluoropyrimidine-based regimens and include gemcitabine with capecitabine, 5-fluorouracil with oxaliplatin (FOLFOX), and 5-fluorouracil with irinotecan (FOLFIRI). The progression-free survival with these regimens averages at 3 months.[24] It is not clear whether these regimens are superior to best supportive care, and this is being investigated currently in the ABC-06 trial that randomizes patients with biliary cancer to second-line FOLFOX versus best supportive care.

Targeted Therapy for Cholangiocarcinoma

Recently, there has been a surge of interest in targeted therapies for intrahepatic cholangiocarcinoma. Next-generation and exome sequencing studies have revealed that 30% to 40% of patients with intrahepatic cholangiocarcinoma have actionable mutations. These include *FGFR* fusions, *IDH*, *BRAF* , and *EGFR* mutations.[25,26] Targeted therapy directed against actionable mutations and identification of molecular subsets with distinct prognostic significance are now feasible in clinical practice. Mutation profiling has highlighted the genomic differences between intrahepatic and extrahepatic cholangiocarcinomas and gallbladder cancer (Table 2). The mutational spectrum of intrahepatic cholangiocarcinoma differs according to geographic location and ethnicity. Chromatin-modulating genes are more commonly mutated in Western patients as compared with Asian patients with liver-fluke-associated cholangiocarcinoma.[27,28] Some of these mutations have prognostic significance. Both *KRAS* and *TP53* mutations are associated with an aggressive disease prognosis, while *FGFR* mutations may signify a relatively indolent disease course of intrahepatic cholangiocarcinoma. During this time, *FGFR* and *IDH* mutations have promising agents in clinical trials.[29] An estimated 10% to 15% of cholangiocarcinomas have DNA repair mutations and may be candidates for immune therapies with checkpoint

inhibitors.[30] Precision medicine clinical trials for intrahepatic cholangiocarcinoma are now a reality and may change the trajectory of this disease. Incorporation of the genomic data into surgical management and multimodality protocols is expected in the near future.

Immune Therapy Approaches

Immune therapy with checkpoint inhibitors has made significant inroads in several human malignancies, particularly those with a high tumor mutational burden, including melanoma, lung cancer, and head and neck malignancies. In gastrointestinal malignancies, tumors with microsatellite instability carry a heavy burden of neoantigens, and immunotherapy is very successful in this setting. Tran et al used a whole-exomic-sequencing-based approach to demonstrate that tumor-infiltrating lymphocytes (TILs) from a patient with metastatic cholangiocarcinoma contained CD4+ T-helper 1 (TH1) cells that recognize a mutation in ERBB2-interacting protein. After adoptive transfer of TILs containing mutation-specific polyfunctional TH1 cells, the patient achieved prolonged partial response. Upon disease progression, the patient was retreated with mutation-reactive TH1 cells and again experienced tumor regression.[31] These results provide evidence that a CD4+ T-cell response against a mutated antigen can lead to tumor regression. Identification of immunogenic epitopes in the mutations seen in cholangiocarcinoma will be key to success with checkpoint inhibitors. Schumacher et al demonstrated that IDH1 (R132 H), seen in 20% of intrahepatic cholangiocarcinoma cases, contains an immunogenic epitope suitable for mutation-specific vaccination.[32] Peptides from the mutated region induce a CD4+ immune response that can potentially be exploited by mutation-specific anti-IDH1 (R132 H) vaccines. Programmed cell death receptor 1 (PDL1) expression has been reported in about 40% of cholangiocarcinoma cases, but mutational tumor burden is generally low. Further immunologic profiling of cholangiocarcinoma is required to identify susceptible cases for immune interventions. Recent results with pembrolizumab in pretreated biliary tract cancers having PDL1 expression indicated that 17% of patients have a meaningful response to checkpoint blockade. These results have reinforced the potential role of immune therapy in this disease.

Conclusions

Intrahepatic cholangiocarcinoma is an aggressive primary cancer of the liver with an adverse prognosis. Upcoming results of multicenter adjuvant therapy trials will provide more conclusive data regarding postoperative therapy after surgical resection, particularly in those at a high risk of recurrence. Advanced stage disease represents a challenge with standard chemotherapy regimens, such as gemcitabine and cisplatin. However, recent genomic data have the potential of altering the disease trajectory with targeted approaches.

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References

1. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. *Oncologist*. 2016;21(5):594-599.
2. Khan SA, Emadossadaty S, Ladep NG, et al. Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? *J Hepatol*. 2012;56(4):848-854.
3. Kinoshita M, Kubo S, Tanaka S, et al. The association between non-alcoholic steatohepatitis and intrahepatic cholangiocarcinoma: a hospital based case-control study. *J Surg Oncol*. 2016; 113(7):779-783.
4. Beyoglu D, Idle JR. The metabolomic window into hepatobiliary disease. *J Hepatol*. 2013;59(4):842-858.
5. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol*. 2014;60(6):1268-1289.
6. Spolverato G, Vitale A, Cucchetti A, et al. Can hepatic resection provide a long-term cure for patients with intrahepatic cholangiocarcinoma? *Cancer*. 2015;121(22):3998-4006.
7. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB (Oxford)*. 2015;17(8):669-680.
8. Jiang W, Zeng ZC, Tang ZY, et al. Benefit of radiotherapy for 90 patients with resected intrahepatic cholangiocarcinoma and concurrent lymph node metastases. *J Cancer Res Clin Oncol*. 2010; 136(9):1323-1331.
9. Li T, Qin LX, Zhou J, et al. Staging, prognostic factors and adjuvant therapy of intrahepatic cholangiocarcinoma after curative resection. *Liver Int*. 2014;34(6):953-960.
10. Li J, Wang Q, Lei Z, et al. Adjuvant transarterial chemoembolization following liver resection for intrahepatic cholangiocarcinoma based on survival risk stratification. *Oncologist*. 2015;20(6): 640-647.
11. Ercolani G, Vetrone G, Grazi GL, et al. Intrahepatic cholangiocarcinoma: primary liver resection and aggressive multimodal treatment of recurrence significantly prolong survival. *Ann Surg*. 2010;252(1):107-114.
12. Sur MD, In H, Sharpe SM, et al. Defining the benefit of adjuvant therapy following resection for intrahepatic cholangiocarcinoma. *Ann Surg Oncol*. 2015;22(7):2209-2217.

13. Miura JT, Johnston FM, Tsai S, et al. Chemotherapy for surgically resected intrahepatic cholangiocarcinoma. *Ann Surg Oncol*. 2015; 22(11):3716-3723.
14. Shinohara ET, Mitra N, Guo M, et al. Radiation therapy is associated with improved survival in the adjuvant and definitive treatment of intrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys*. 2008;72(5):1495-1501.
15. Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer*. 2002;95(8): 1685-1695.
16. Neoptolemos JP, Moore MJ, Cox TF, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA*. 2012;308(2):147-156.
17. Horgan AM, Amir E, Walter TE Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol*. 2012;30(16):1934-1940.
18. Stein A, Arnold D, Bridgewater J, et al. Adjuvant chemotherapy with gemcitabine and cisplatin compared to observation after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma (ACTICCA-1 trial) - a randomized, multidisciplinary, multinational phase III trial. *BMC Cancer*. 2015;15:564.
19. Valle JW, Wasan H, Johnson P, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study—The UK ABC-01 Study. *Br J Cancer*. 2009;101(4):621-627.
20. Valle JW, Wasan H, Lopes A, et al. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. *Lancet Oncol*. 2015;16(8):967-978.
21. Malka D, Cervera P, Foulon S, et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. *Lancet Oncol*. 2014;15(8):819-828.
22. Crane CH, Koay EJ. Solutions that enable ablative radiotherapy for large liver tumors: fractionated dose painting, simultaneous integrated protection, motion management, and computed tomography image guidance. *Cancer*. 2016;122(13):1974-1986.
23. Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol*. 2016;34(5): 460-468.
24. Rogers JE, Law L, Nguyen VD, et al. Second-line systemic treatment for advanced cholangiocarcinoma. *J Gastrointest Oncol*. 2014;5(6):408-413.
25. Jain A, Kwong LN, Javle M. Genomic profiling of biliary tract cancers and implications for clinical practice. *Curr Treat Options Oncol*. 2016;17(11):58.
26. Jain A, Javle M. Molecular profiling of biliary tract cancer: a target rich disease. *J Gastrointest Oncol*. 2016;7(5):797-803.
27. Ong CK, Subimerb C, Pairojkul C, et al. Exome sequencing of liver fluke-associated cholangiocarcinoma. *Nat Genet*. 2012; 44(6):690-693.
28. Jiao Y, Pawlik TM, Anders RA, et al. Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas. *Nat Genet*. 2013; 45(12):1470-1473.
29. Churi CR, Shroff R, Wang Y, et al. Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. *PLoS One*. 2014;9(12):e115383.
30. Ahn DH, Javle M, Ahn CW, et al. Next-generation sequencing survey of biliary tract cancer reveals the association between tumor somatic variants and chemotherapy resistance. *Cancer*. 2016;122(23):3657-3666.
31. Tran E, Turcotte S, Gros A, et al. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. *Science*. 2014;344(6184):641-645.
32. Schumacher T, Bunse L, Pusch S, et al. A vaccine targeting mutant IDH1 induces antitumour immunity. *Nature*. 2014; 512(7514):324-327.
33. Nakamura H, Arai Y, Totoki Y, et al. Genomic spectra of biliary tract cancer. *Nat Genet*. 2015;47(9):1003-1010.
34. Zou S, Li J, Zhou H, et al. Mutational landscape of intrahepatic cholangiocarcinoma. *Nat Commun*. 2014;5:5696.
35. Javle M, Bekaii-Saab T, Jain A, et al. Biliary cancer: utility of next-generation sequencing for clinical management. *Cancer*. 2016;122(24):3838-3847.
36. Simbolo M, Fassan M, Ruzzenente A, et al. Multigene mutational profiling of cholangiocarcinomas identifies actionable molecular subgroups. *Oncotarget*. 2014;5(9):2839-2852.