Adjuvant Therapy is Associated with Improved Survival After Curative Resection for Hilar Cholangiocarcinoma: A Multi-Institution Analysis from the U.S. Extrahepatic Biliary Malignancy Consortium

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Abstract

Background—Curative-intent treatment for localized hilar cholangiocarcinoma (HC) requires surgical resection. However, the effect of adjuvant therapy (AT) on survival is unclear. We analyzed the impact of AT on overall (OS) and recurrence free survival (RFS) in patients undergoing curative resection.

Methods—We reviewed patients with resected HC between 2000 and 2015 from the ten institutions participating in the U.S. Extrahepatic Biliary Malignancy Consortium. We analyzed

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the impact of AT on RFS and OS. The probability of RFS and OS were calculated in the method of Kaplan and Meier and analyzed using multivariate Cox regression analysis.

Results—A total of 249 patients underwent curative resection for HC. Patients who received AT and those who did not had similar demographic and preoperative features. In a multivariate Cox regression analysis, AT conferred a significant protective effect on OS (HR 0.58, p=0.013), and this was maintained in a propensity matched analysis (HR 0.66, p=0.033). The protective effect of AT remained significant when node negative patients were excluded (HR 0.28, p=0.001), while it disappeared (HR 0.76, p=0.260) when node positive patients were excluded.

Conclusions—Adjuvant therapy should be strongly considered after curative-intent resection for hilar cholangiocarcinoma, particularly in patients with node positive disease.

Keywords

adjuvant therapy; hilar cholangiocarcinoma; chemotherapy; biliary cancer; survival

Introduction

Cholangiocarcinoma accounts for 3% of gastrointestinal malignancies worldwide, with 3500 cases diagnosed per year in the United States, the majority of which (60-80%) arise in the perihilar region.[1,2] Unresectable disease has a dismal prognosis, with a median survival of less than one year.[1,3] Margin negative R0 resection provides the only chance for long-term cure.[3,4] Despite this, resectable disease has a five-year survival between 20 and 50%.[3,5–7] Adjuvant therapy (AT) has been advocated after resected hilar cholangiocarcinoma (HC) to improve outcomes.[8–10]

The role of AT for resected HC is a source of significant debate.[11] Current National Comprehensive Cancer Network (NCCN) guidelines for AT in resected HC comment that more data is necessary in order to make firm conclusions.[12] In two recent retrospective reviews of AT in biliary tract cancer (BTC), no survival benefit was found.[7,13] Conversely, within the last ten years three single center retrospective studies have demonstrated a survival benefit with AT in resected extrahepatic cholangiocarcinoma.[8–10] In the only published phase III randomized trial of AT that included patients with HC, and in the recently completed phase III trial of gemcitabine plus oxaliplatin in BTC, there was no significant survival benefit noted.[14,15]

Herein, we sought to determine the role of AT in resected HC by evaluating a large group of patients undergoing treatment with curative intent from the U.S. Extrahepatic Biliary Malignancy Consortium. We hypothesized that AT would improve both and recurrence free (RFS) overall survival (OS) in resected HC.

Methods

Patient Population

Our data source included all patients who underwent operative intervention with curative intent for extrahepatic biliary malignancy from January 2000 to April 2015 from ten institutions participating in the U.S. Extrahepatic Biliary Malignancy Consortium: Emory

University, The Johns Hopkins University, Stanford University, Vanderbilt University, Washington University in St Louis, University of Wisconsin, University of Louisville, Wake Forest University, The Ohio State University, and New York University. Institutional Review Board approval for the study was obtained at all participating institutions.

All patient characteristics, operative/treatment data, and clincopathological data were gathered retrospectively via chart review (Table 1). Medical comorbidities, as coded via chart review, included: hypertension, diabetes, cardiac history, congestive heart failure, dyspnea, smoking history, severe chronic obstructive pulmonary disease (COPD), on a ventilator, acute renal failure, dialysis, chronic steroid use, disseminated cancer, and primary sclerosing cholangitis. We included all patients identified as undergoing a completed curative type resection for HC, excluding R2 resections. We analyzed the impact of AT on the primary outcome of OS and secondary outcome of RFS. OS was measured from the time of resection to death or last follow-up on chart review. Date of death was determined via chart review or the Social Security Death Index. RFS was defined as time from initial resection to recurrence, final documented follow up or death.

Statistical Methods

The probability of OS and RFS were calculated in the method of Kaplan and Meier and analyzed using multivariate Cox regression analysis.[16,17] Multivariate modeling was used to assess the impact of selected variables on both OS and RFS. Clinical judgment was used to select variables to evaluate from our dataset on univariate survival analysis, and these same variables were applied to our multivariate survival analysis. Patients who received AT were propensity score matched to patients who did not in a 1:1 ratio using variables which were found to be significantly associated with survival following resection (i.e. patient age, ASA, lymph node status, and grade) in the multivariable analysis. Propensity score matching was accomplished using a greedy matching algorithm with a caliper distance of 0.2 standard deviations of the logit of the propensity score.

Characteristics of the patient population receiving and not receiving AT were compared. Categorical variables were compared using the Fisher exact test or χ^2 test as appropriate, and continuous variables were compared using the two-tailed t test. Statistical significance was set at p<0.05. STATA version 13.1 (StataCorp LP, College Station, TX, USA) was used for data analysis.

Results

Patient Population and Baseline Characteristics

249 patients underwent resection with curative intent for HC. In 224 patients (90%) AT status was known (129 receiving AT and 95 who did not). Baseline characteristics (age, sex, race, ASA classification, medical comorbidities, neo-adjuvant therapy status) were similar between groups (Table 1). A breakdown of AT status and type is depicted in Figure 1.

Operative and Pathological Data

The operative and pathology data is presented in Table 1. There was no significant difference seen between groups for method of operation, AJCC T stage, presence of lymphovascular invasion, tumor grade and completion of preoperative diagnostic laparoscopy.[18] As depicted in Table 1, those in the AT group tended to have more bile duct resections only or left hepatectomies (*p=0.017*), were more likely to have a positive frozen section (*p=0.015*), were less likely to receive an intraoperative blood transfusion (*p=0.001*), had a greater percentage of R1 resections (*p=0.012*), and had a greater rate of lymph node (LN) positivity (*p<0.001*). The mean number of LNs examined was similar between the no AT (4.47 ± 0.41) and AT (4.62 ± 0.46) groups (p=0.811).

Postoperative Data

Postoperatively, 90 day hospital readmission and location of recurrent disease were similar between groups. Length of stay was significantly greater in the no AT group at 19.5 ± 1.8 days, versus 11.2 ± 0.5 days in the AT group (*p<0.001*). See table 1 for more details.

Adjuvant Therapy Details

In the AT group (N=129), 89 patients (69%) received combined chemoradiotherapy, 35 patients (27%) received only chemotherapy, and 5 patients (4%) received only radiation therapy (Figure 1). See Figure 1 for further information regarding chemotherapy regimen.

Univariate Analysis of RFS/OS

Median follow up after resection for the group was 19.8 months. RFS for the group as a whole was 13.5% at 5 years, with a 16.3 month median RFS. OS for the group was 17.0% at 5 years, with a median OS of 21.7 months. For the no AT group RFS at 5 years was 14.3%, with a median RFS of 13.3 months, while for the AT group 5 year RFS was 11.0%, with a 17.4 month median RFS (p=0.25). For the no AT group OS at 5 years was 21.3%, with a median 20.0 month OS, while for the AT group 5 year OS was 14.2%, with a 21.9 month median OS (p=0.25).

LN positivity, age 60 years old, and worse tumor grade were all associated with decreased RFS, Table 2. Factors associated with decreased OS on univariate analysis include: LN positivity, and age 60 years old. Tumor size greater than 2cm, non-R0 resection status, increased ASA class, comorbidities, and concomitant liver resection had no significant association with RFS or OS. Tumor grade had no significant relationship with OS.

Multivariate Cox Regression Modeling of RFS

Utilizing multivariate cox regression analysis we created a model to evaluate RFS and OS (Table 2). AT, tumor size >20mm, LN positivity, resection status (R1 versus R0), increased age, higher ASA status (III/IV), comorbidities, concomitant liver resection, and tumor grade (moderate, poor or undifferentiated) were included in the model. Of these variables, AT (*p=0.005*, HR 0.55) and higher ASA status (*p=0.003*, HR 0.54) were found to be significantly predictive of improved RFS. LN positive final pathology (*p=0.001*, HR 2.06), increased age (*p=0.005*, HR 1.02), poorly differentiated pathology (*p=0.015*, HR 1.89), and

undifferentiated pathology (*p=0.025*, HR 10.53) were all found to be significantly predictive of worse RFS. Tumor size >20mm (p=0.140, HR 1.36), R1 versus R0 resection status (p=0.720, HR 1.08), presence of comorbidities (p=0.420, HR 1.161), concomitant liver resection (p=0.70, HR 1.09), and moderately differentiated pathology (p=0.597, HR 1.13) were found to be non-significant predictors of RFS on multivariate analysis.

Multivariate Cox Regression Modeling of OS

AT (*p=0.014*, HR 0.58) was found to significantly predict improved OS. The benefit seen with AT on OS is further displayed in Table 2. LN positive final pathology (*p=0.002*, HR 1.95), increased age (*p=0.011*, HR 1.02), and undifferentiated pathology (*p=0.029*, HR 9.97) were all found to significantly predict decreased OS. Tumor size >20mm (p=0.587, HR 1.12), R1 versus R0 resection status (p=0.372, HR 1.21), higher ASA classification (p=0.073, HR 0.69), concomitant liver resection (p=0.727, HR1.08), moderately differentiated pathology (p=0.573, HR 1.14), and poorly differentiated pathology (p=0.166, HR1.44) were found to be non-significant predictors of OS on multivariate analysis.

Propensity Matching of AT and no AT Groups

We next matched patients who received AT to those who did not based on age, LN status, ASA, and tumor grade using propensity scores (Supplemental Table). We matched based on these variables because they were the only independent predictors of survival in our multivariate analysis (Table 2) other than AT. As displayed in Figure 2, matched patients who received AT had significantly improved RFS (17.7 months vs 10.9 months, *p=0.015*, HR 0.61), as well as OS (21.5 months vs 13.5 months, *p=0.033*, HR 0.66).

Multivariate Cox Regression Modeling Subgroup Analysis of OS

The multivariate analysis was redone separating chemotherapy and chemoradiotherapy, with both groups demonstrating a similar OS benefit (both HR 0.6) to the combined analysis shown in table 2 (HR 0.58). When only LN positive patients were included in the multivariate model, AT continued to be associated with improved OS (HR 0.28, *p=0.001*). When only node negative patients were included in the model, AT was no longer significantly associated with improved OS (HR 0.76, p=0.26).

Discussion

To our knowledge, our current analysis represents the largest in a Western cohort that explores the role of AT on outcomes in resected HC. The majority of the patients in our study who underwent AT received both chemotherapy and radiation therapy (69%), with 27% only receiving chemotherapy and the rest only radiation therapy. Although AT had no survival benefit on univariate analysis, likely reflecting the increased rate of nodal positivity and R1 resection margin in this group (Table 1), on multivariate analysis as well as on a propensity matched analysis (Figure 2), we demonstrated an association between having received AT, and improved OS and RFS. This relationship disappeared when removing the node positive patients from the multivariate analysis. Therefore, we are able to draw the conclusion that adjuvant chemo/chemoradiotherapy is significantly associated with

improved survival in patients undergoing curative resection for HC who harbor positive LNs on final pathology.

The only published phase III randomized trial that evaluated AT in HC was from 2002 by Takada et. al.[14] This study of 508 patients with pancreaticobiliary malignancies, enrolled from 1986-1992, included 139 patients with cholangiocarcinoma, and randomly assigned patients to surgery alone or surgery with adjuvant mitomycin C plus 5-fluoruracil. They demonstrated no significant survival benefit in the cholangiocarcinoma cohort (OS AT 26.7% vs. 24.1% no AT at 5 years). In contrast to this study, our present analysis evaluates a more modern cohort of patients representing contemporary surgical outcomes (see Table 3 for further comparison details).

A 2016 Korean retrospective study, that included 260 patients with resected HC, demonstrated no survival benefit with a predominantly fluorouracil based AT regimen, with an OS of 21.2% at 5 years for those receiving AT, versus 16.7% for those not receiving AT.[7] A survival benefit was noted in the node positive cohort. A 2011 retrospective analysis that included 50 patients with HC demonstrated benefit with adjuvant chemotherapy (OS 47% AT vs. 36% no AT at 5 years), and similar to our study this benefit was limited to the node positive group.[10] A meta-analysis from Horgan et. al. included 6,712 patients with BTC, and although there was no improvement in survival for patients receiving AT after surgical resection, again, in line with our data, a survival benefit was seen in patients with node positive disease.[19] The recently released results from the phase III PRODIGE 12-ACCORD 18 European randomized controlled trial of adjuvant gemcitabine plus oxaliplatin in resected BTC demonstrated no impact of AT on survival in HC, even in those with node positive disease.[15] This trial was limited by the small number of patients with HC accrued (N=15).

Of note, the 5-year median survival of 21.7 months in our patient cohort is lower than prior studies. This is likely reflective of different patient populations with variable tumor biology. For instance, our mean age was 65±11 years. Takada et. al. excluded patients 75 years or older and had a mean population age of 61, similar to other studies.[7,14,20,21] In addition, each study represented a different population with specific exclusion criteria.[9,14,20,21] Furthermore, tumor characteristics differ widely between studies. For example, the SWOG 0809 phase II trial had an R1 resection margin in 32% of patients and Kim et. al. had 0 patients with a positive resection margin.[9,21] For our study, 40% of patients in the AT group had an R1 resection. Finally, prior studies have included a heterogeneous population of pancreaticobiliary malignancies, while ours is one of the only to focus solely on HC.[8–10,13,14,19–22]

Our data is in line with a study from Matsuo et. al., who examined 157 patients with resected HC, and showed that LN positivity and worse tumor grade imparted significantly decreased survival.[4] Our demonstration of decreased OS and RFS for patients with positive LNs is consistent with many prior studies.[4,7,9,10] Matsuo et. al. also linked concomitant hepatectomy with improved survival for HC, although this was not supported by our data.[4]

Of note, R0 resection was not an independent predictor of improved survival on multivariate analysis. This contrasts with prior reports.[3,4,10] However, it is consistent with other data that

demonstrated no appreciable independent benefit with R0 resection.[7,20,21] Our lack of benefit for R0 resection may be due to the relatively high use of AT, which was more likely to be used after an R1 resection. In addition, our rate of node positive resection for the cohort was 37%, which is comparable to several prior studies, but is significantly greater than others, such as the retrospective study by Kang et. al. that reported a 25% LN positivity rate.[7,8,10]

Our study is limited by its retrospective nature. Although we strived to created concise definitions across the member institutions that would easily allow translation from each hospital system, we acknowledge that there are cases where the coded data would likely differ depending upon the reviewer. In addition, we recognize that the 15 year collection period over multiple centers leads to considerable patient and treatment heterogeneity. Although we acknowledge these drawbacks to our dataset, the relatively large number of patients included in our study, in combination with the fact that 2000-2015 represents a more modern cohort than most prior Western studies, we do feel that our analysis fills a significant gap in the literature.[13,22] Our data also lacks significant detail regarding chemotherapy regimens (see Figure 1), with only 34% of the patients receiving chemotherapy in our database having a defined regimen. This is a function of the limited granularity afforded by our retrospective database. Although we feel that these missing 66% of regimens from 10 academic centers from 2000 to the present likely represent variations of fluorouracil/gemcitabine based therapy, we are unable to make strong specific recommendations. Our conclusions are strengthened by our propensity matched analysis, and although the number of patients was insufficient to match for all preoperative variables, we were able to match for all variables that were significant in our multivariate model.

NCCN guidelines make no definitive AT recommendations for resected HC, but rather comments on observation versus fluoropyrimidine based chemoradiation versus gemcitabine or fluoropyrimidine based chemotherapy.[12] For advanced or metastatic disease, recent data demonstrated a survival benefit with gemcitabine plus oxaliplatin as compared to fluorouracil (4.6 vs. 9.5 month, for fluorouracil and gemcitabine plus oxaliplatin groups, respectively), and a pooled analysis of clinical trials from 2007 also supported the combination of gemcitabine plus platinum based chemotherapy.[23,24] Gemcitabine plus cisplatin has a category 1 recommendation per NCCN guidelines for advanced/metastatic disease.[12] Our data supports the use of AT after resection of node positive HC, and with the adoption of updated chemotherapy regimens we are hopeful for future improvement in survival.

Our multi-institutional study of 249 patients who underwent resection for HC, shows an association of AT and improved survival both on multivariate and propensity matched analysis, with the effect limited to those with node positive disease. It is likely that with the discovery of more active regimens in HC, AT will be more effective and incorporated into future treatment protocols.[25–27]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Synopsis

Adjuvant therapy is an independent predictor of improved survival in resected hilar cholangiocarcinoma. Adjuvant therapy should be strongly considered after curative-intent resection for hilar cholangiocarcinoma, particularly in patients with node positive disease.
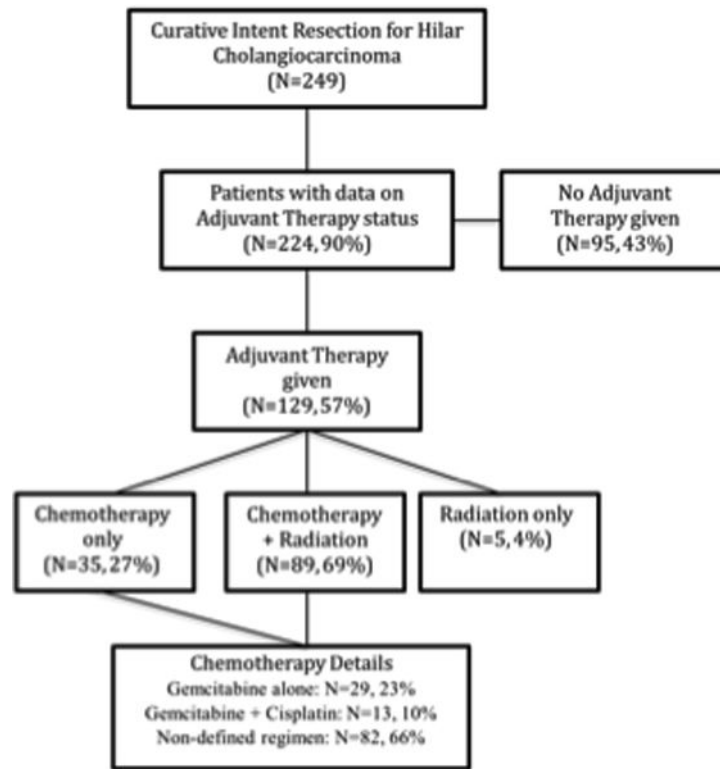
FIGURE 1.
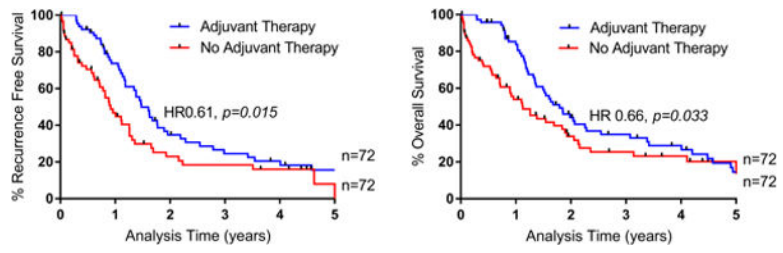Breakdown of Patients by Adjuvant Therapy Type

FIGURE 2.
Overall and Recurrence Free Survival Based on Adjuvant Therapy Status for Propensity
Matched Patients

TABLE 1

Association of Pretreatment, Surgery and Pathology Variables with Adjuvant Therapy

Variable	No AT (n=95, 42%)		AT (n=129, 58%)		p
	N	%	N	%	
Pretreatment Data					
Age (mean and SD)[*]	66	10	64	12	0.180
Male	53	56	82	64	0.240
Race					0.162
Caucasian	73	77	105	82	
Other	22	23	24	19	
ASA					0.432
1	1	1	1	1	
2	23	29	42	38	
3	50	64	66	59	
4	4	5	2	2	
Comorbidities[a]					0.141
Yes	63	66	56	43	
No	32	34	73	57	
Neo-adjuvant Therapy	6	6	4	3	0.250
Operative and Pathology Data					
Diagnostic Laparoscopy	19	20	16	`1	0.128
Type of Operation					*0.017*
BD Resection Only	16	17	35	28	
Right Hepatectomy and BD	17	18	8	6	
Left Hepatectomy and BD	16	17	35	28	
Extended Right Hepatectomy and BD	20	21	16	13	
Extended Left Hepatectomy and BD	6	6	12	9	
Right Trisectionectomy and BD	10	10	12	9	
Left Trisectionectomy and BD	9	10	9	7	
Method of Operation[a]					0.177
Open	93	98	128	99	

Variable	No AT (n=95, 42%)		AT (n=129, 58%)		p
	N	%	N	%	
Laparoscopic	0	0	1	1	
Converted to Open	2	2	0	0	
Frozen Section +	24	29	49	46	0.015
Intraoperative RBCs	45	54	35	30	0.001
R Status					0.012
R0	71	75	77	60	
R1	24	25	52	40	
AJCC 7th. ed. T Stage[18]					0.803
T1	29	31	36	28	
T2	47	49	72	56	
T3	15	16	17	13	
T4	4	4	4	3	
Grade of Differentiation					0.237
Well	12	15	25	20	
Moderate	53	65	69	55	
Poor	15	19	32	25	
Undifferentiated	1	1	0	0	
LVI	27	34	49	45	0.124
LN Positive	17	20	55	49	<0.001
	Postoperative Data				
Readmission 90 Days	24	41	28	32	0.923
Recurrence Location[b]					0.198
Local	12	43	15	24	
Distant	11	39	31	50	
Local + Distant	5	18	16	26	

Abbreviations: AT, adjuvant therapy; SD, standard deviation; ASA, American Society of Anesthesiologists classification system; BD, bile duct; R status, resection status; AJCC, American Joint Committee on Cancer; LVI, lymphovascular invasion; LN, lymph node.

*
For Age: columns n and % signify mean and standard deviation, respectively

a
Comorbidities determined via chart review, as discussed in methods section

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[b] % reflects percentage of the total number of patients that had a recurrence

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TABLE 2

Significant Relationships on Univariate Analysis and Multivariate Cox Regression Analysis for Recurrence Free and Overall Survival

| | | Univariate Analysis | | | | |
| | | RFS | | OS | | |
	N	Median Survival (mo)	p value	Median Survival (mo)	p value	
LN Status			0.004		0.011	
Negative	136	17.3		24.3		
Positive	81	13.7		17.6		
Age			0.044		0.008	
<60 yrs	72	20.1		27.8		
60 yrs	176	15.0		18.2		
Grade			0.022		0.081	
Well Diff.	43	20.0		27.8		
Mod Diff.	132	16.0		19.3		
Poorly Diff.	53	12.5		22.2		
Undifferentiated	1	–		4.8		

| | Multivariate Analysis | | | |
| | RFS | | OS | |
	p	aHR (95% CI)	p	aHR (95% CI)
Adjuvant Therapy	0.005	0.55 (0.37-0.84)	0.013	0.58 (0.38-0.89)
LN Positive	0.001	2.06 (1.39-3.04)	0.002	1.95 (1.28-2.95)
Age (Increasing)	0.005	1.02 (1.01-1.04)	0.011	1.02 (1.01-1.04)
ASA Status (Higher[*])	0.003	0.54 (0.37-0.81)	0.073	0.69 (0.46-1.04)
Grade (vs. Well Diff.)				
Mod Diff.	0.597	1.13 (0.72-1.76)	0.573	1.14 (0.72-1.80)
Poorly Diff.	0.015	1.89 (1.13-3.16)	0.166	1.44 (0.86-2.43)
Undifferentiated	0.025	10.53 (1.34-82.74)	0.029	9.97 (1.26-78.94)

Abbreviations: RFS, recurrence free survival; OS, overall survival; N, number at risk; mo, months; LN, lymph node; R status, resection status; yrs, years; Mod, moderately; Diff., differentiated; aHR, adjusted hazard ratio; ASA, American Society of Anesthesiologists classification system.

*
ASA Higher signifies ASA class of 3 or greater

TABLE 3

Studies Evaluating Adjuvant Chemotherapy ± Radiation for Resected Hilar Cholangiocarcinoma

Investigator/Year	Country	Type Study	Years Data	# EHBTC/ Total # Study	% Total Hilar	% AT	5 year % OS AT	OS AT (months)	AT Regimen	Improved Survival with AT?	Improved Survival AT-Node Positive Subset?
Takada[14] 2002	JAPAN	Phase III RCT, multicenter	1986-1992[a]	139[b]/508	–	50	26.7[c]	–	MMC + 5FU	No	–
Borghero[22] 2008	USA	Retro, single center[d]	1984-2005	65/65	55	65[e]	36	31	ChemoXRT (5FU based)	–	–
Lim[8] 2009	KOREA	Retro, single center	2000-2006	120/120	49	75	(3yr) 62.6	–	CCRT vs. CCRT+ 5FU based chemo	Yes	No
Kim[9] 2011	KOREA	Retro, single center	2001-2009	168/168	53.9	68	36.5	–	5FU/LCV + XRT	Yes	Yes
Murakami[10] 2011	JAPAN	Retro, single center	1990-2009	106/127	39	39	47	–	GEM based	Yes	Yes
Park[20] 2011	KOREA	Retro, single center	1998-2007	101/101	35	84	34	24	All XRT, 84% chemo (most CAP based)	–	–
Glazer[13] 2012	USA	Retro, single center	1978-2009	40/197	–	49.1	–	46/53[f]	CAP/GEM based, 15.3% ChemoXRT	No	–
Horgan[19] 2012	N/A	Meta-analysis	1960-2010	–/6712	–	–	–	–	Multiple regimens	No	Yes
Ben-Josef[21] 2015	USA	Phase II Trial, multicenter	2008-2012[a]	35/79	48	86[g]	(2yr) 65	35	GEM + CAP, 87% also XRT	–	–
Kang[7] 2016	KOREA	Retro, single center	1991-2010	260/260	100	48.8	21.2	24.8	ChemoXRT (5FU based), some just XRT/ chemo	No	Yes
Edeline[15] 2017	EUROPE	Phase III RCT, multicenter	2009-2014	69/193	8	–	–	–	GEM + OX	No	No

Abbreviations: EHBTC, extra hepatic biliary tract cancer; AT, adjuvant therapy; OS, overall survival; RCT, randomized controlled trial; MMC, mitomycin C; 5FU, 5-fluorouracil; retro, retrospective; chemoXRT, chemotherapy and radiation therapy; CCRT, concurrent chemoradiotherapy; LCV, leucovirin; XRT, radiation therapy; GEM, gemcitabine; CAP, capecitabine; OX, oxaliplatin.

[a]Years patients enrolled

[b] Intrahepatic cholangiocarcinoma included in group with no exact numbers given

[c] For extrahepatic cholangiocarcinoma group

[d] Most at a single center

[e] Only R1 and/or N1 underwent chemoXRT

[f] 46/53 month med survival chemo/chemoXRT groups

[g] % completed