Survival Benefit With Adjuvant Radiotherapy After Resection of Distal Cholangiocarcinoma: A Propensity-Matched National Cancer Database Analysis

Sivesh K. Kamarajah, BMedSci, MBChB [1,2,3]; Filip Bednar, MD, PhD[4]; Clifford S. Cho, MD[4]; and Hari Nathan, MD, PhD[4]

BACKGROUND: No convincing evidence for the benefit of adjuvant radiotherapy (RT) following resection of distal cholangiocarcinoma (dCCA) exists, especially for lower-risk (margin- or node-negative) disease. Hence, the association of adjuvant RT on survival after surgical resection of dCCA was compared with no adjuvant RT (noRT). **METHODS:** Using National Cancer Database data from 2004 to 2016, patients undergoing pancreatoduodenectomy for nonmetastatic dCCA were identified. Patients with neoadjuvant RT and chemotherapy and survival <6 months were excluded. Propensity score matching was used to account for treatment-selection bias. A multivariable Cox proportional hazards model was then used to analyze the association of adjuvant RT with survival. **RESULTS:** Of 2162 (34%) adjuvant RT and 4155 (66%) noRT patients, 1509 adjuvant RT and 1509 noRT patients remained in the cohort after matching. The rates of node-negative disease (N0), node-positive disease (N+), and unknown node status (Nx) were 39%, 51%, and 10%, respectively. After matching, adjuvant RT was associated with improved survival (median, 29.3 vs 26.8 months; $P < .001$), which remained after multivariable adjustment (HR, 0.86; 95% CI, 0.80-0.93; $P < .001$). Multivariable interaction analyses showed this benefit was seen irrespective of nodal status (N0: HR, 0.77; 95% CI, 0.66-0.89; $P < .001$; N+: HR, 0.79; 95% CI, 0.71-0.89; $P < .001$) and margin status (R0: HR, 0.58; 95% CI, 0.50-0.67; $P < .001$; R1: HR, 0.87; 95% CI, 0.78-0.96; $P = .007$). Stratified analyses by nodal and margin status demonstrated consistent results. **CONCLUSIONS:** Adjuvant RT after dCCA resection was associated with a survival benefit in patients, even in patients with margin- or node-negative resections. Adjuvant RT should be considered routinely irrespective of margin and nodal status after resection for dCCA. ***Cancer* 2021;127:1266-1274**. © *2020 American Cancer Society*.

LAY SUMMARY:

- Adjuvant radiotherapy after resection of distal cholangiocarcinoma was associated with a survival benefit in patients, even in patients with margin-negative or node-negative resections.
- Adjuvant radiotherapy should be considered routinely irrespective of margin and nodal status after resection of distal cholangiocarcinoma.

KEYWORDS: chemotherapy, distal cholangiocarcinoma, radiotherapy, resection, survival.

INTRODUCTION

Despite advances in multimodal treatment, distal cholangiocarcinoma (dCCA) has poor 5-year survival rates ranging from 20% to 50%, even after resection.[1-6] Because local recurrence rates may be as high as 50%,[7,8] incorporation of chemotherapy (CT) has been the focus of study, and a recent randomized controlled trial has demonstrated a survival benefit with adjuvant systemic CT.[9] However, the benefit of routine adjuvant radiotherapy (RT) has been questionable.[10] In contrast to pancreatic cancer, in which accumulating evidence from retrospective series[10-12] suggests some survival benefit of adjuvant RT, the role of adjuvant RT in biliary tract malignancy remains unclear.

To date, high-quality evidence on adjuvant RT for dCCA is lacking. First, the rarity of dCCA means recruitment to RCTs is difficult, and no single RCT focused on adjuvant RT in dCCA exists. Second, current evidence—limited to retrospective single-center, multi-institutional series—offers conflicting evidence regarding the benefit of adjuvant RT.[13-16] As a result, current clinical practice is guided by evidence from RCTs[9,10,17-22] and meta-analyses[23-25] of biliary tract cancers that are conflicting. Because different biliary tract cancer subtypes (ie, intrahepatic, hilar, and distal) have varying prognoses, genetic profiles, and possibly responses to adjuvant RT, findings from subgroup analyses for dCCA within these RCTs are often underpowered. Therefore, the use of adjuvant RT after resection of dCCA remains controversial, especially in patients thought to be at lower risk for local recurrence, such as those with margin-negative resections and node-negative disease.

Corresponding Author: Hari Nathan, MD, PhD, Department of Surgery, University of Michigan, 2210A Taubman Health Care Center, 1500 E Medical Center Dr, SPC 5343, Ann Arbor, MI 48109-5343 (drnathan@umich.edu).

[1]Department of HPB and Transplant Surgery, Freeman Hospital, Newcastle Upon Tyne, Tyne and Wear, United Kingdom; [2]Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, Tyne and Wear, United Kingdom; [3]Department of Surgery, Queen Elizabeth Hospital Birmingham, University Hospital Birmingham NHS Trust, Birmingham, United Kingdom; [4]Department of Surgery, University of Michigan, Ann Arbor, Michigan

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33356, **Received:** October 13, 2020; **Revised:** November 7, 2020; **Accepted:** November 10, 2020, **Published online** December 15, 2020 in Wiley Online Library (wileyonlinelibrary.com)

We sought to add evidence to this debate by performing a large, nationwide, high-quality retrospective study to assess the potential benefit of adjuvant RT after resection of dCCA. With contemporary data from the National Cancer Data Base (NCDB), we analyzed the association of adjuvant RT with survival after resection of dCCA with landmark analyses performed in patients surviving >6 months to account for immortal time bias. We used propensity-matched analysis to address treatment-selection bias; we also assessed survival in clinically relevant subgroups of patients based on nodal and margin status.

MATERIALS AND METHODS

Data Source

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society.[26,27] The NCDB gathers information from approximately 1500 CoC-accredited hospitals and includes >70% of all newly diagnosed malignancies in the United States. It contains specific details about patient demographics (age, sex, race, and payer), facility type and location, tumor characteristics (size, grade, stage, and histology), treatment course (type of surgery, receipt of CT, and receipt of adjuvant RT), and outcomes (resection margins, lymph node status, and vital status).

Study Population

The NCDB was used to identify all patients >35 years old diagnosed with nonmetastatic dCCA undergoing pancreatoduodenectomy between 2004 and 2016. The *International Classification of Disease for Oncology* (Third Edition) classifications were used to select adenocarcinoma histology and exclude mucinous tumors, neuroendocrine tumors, and other histologies. Patients with other concomitant cancer diagnoses, those for whom dCCA was not their first cancer, those who received neoadjuvant CT or RT, and patients with missing data on lymph node status were excluded. In addition, patients with survival <6 months (n = 600) were excluded to account for immortal time bias, as previously described.[11,28]

We analyzed the following patient-level characteristics as provided by the NCDB: age (36-50, 51-65, 66-80, >80 years), race (White, Black, other), Charlson-Deyo combined comorbidity score, year of diagnosis, insurance status (Medicaid/Medicare, private insurance, uninsured), zip code-level education status (<7%, 7%-12.9%, 13%-20.9%, ≥21%), zip-code–level median household income (<$48,000, $48,000-$62,999, ≥$63,000), and urban versus rural area of residence. The zip-code–level education status represents the proportion of adults in the patient's zip code who did not graduate from high school and is categorized as equally proportioned quartiles among all US zip codes. We also analyzed the following hospital-level characteristics: facility type (academic, community, other), facility location (the Midwest, Northeast, South, or West), and hospital distance from patient (<12.5 miles, 12.5-49.9 miles, ≥50 miles). Finally, we analyzed the following clinicopathologic characteristics: nodal status (N0 = node-negative disease, N+ = node-positive disease, Nx = unknown node status), tumor grade/differentiation (well/moderate, poor/anaplastic, unknown), lymphovascular invasion (absent, present), and margin status (positive, negative).

Finally, we analyzed receipt of adjuvant RT versus no adjuvant RT (noRT) as the primary exposure variable. Coding for adjuvant therapy (ie, CT or RT) was derived using the start of adjuvant therapy (ie, CT or RT) from diagnosis and surgery to obtain reliable estimates. However, discrimination between adjuvant RT-sensitizing CT was not possible based on the current available data.

Statistical Analysis

Categorical variables were compared using the chi-squared test. Nonnormally distributed data were analyzed using the Mann-Whitney *U* test. Survival was estimated using Kaplan-Meier survival curves and compared using the log-rank test. Multivariable analyses used Cox proportional hazards models. The conditional probability of receiving adjuvant RT—the propensity score—was estimated using a multivariable logistic regression model including all patient- and hospital-level variables listed above. Next, we created balanced cohorts using 1-to-1 nearest-neighbor propensity score matching (PSM) without replacement (caliper width, 0.1 SD).[29] Balance diagnostics were conducted by using standardized mean differences, with a value <0.1 indicating good balance.[29] We then evaluated overall survival of matched patients with and without adjuvant CT. To address any residual confounding after PSM, multivariable Cox proportional hazards models again adjusted for all variables listed above from the propensity-matched cohort. A stratified survival analysis by lymph node and margin status and interaction analyses between adjuvant RT and lymph node and margin status were performed. Sensitivity landmark analyses were performed in patients surviving >6 months to account for immortal time bias. A *P* value of <.05 was considered statistically significant. Data analysis was performed using R Foundation software (R 3.2.2 version; R Foundation for

Statistical Computing, Vienna, Austria; https://www.r-project.org/) with TableOne, ggplot2, Hmisc, Matchit, and survival packages as previously described.[11] The study protocol was deemed exempt from review by the University of Michigan Institutional Review Board.

RESULTS

Patient Demographics and Clinicopathologic Characteristics

This study included 6317 patients with surgically resected dCCA. Of these patients, 2162 (34%) received adjuvant RT and 4155 (66%) had noRT. Median follow-up was 19 months (interquartile range, 10-33 months). Baseline demographics of the unmatched cohort confirmed that patients receiving adjuvant RT were younger and had lower comorbidity burden (Table 1). There was also a variation in the receipt of adjuvant RT between centers from 0% to 100% (Supporting Fig. 1). The median number of lymph nodes examined in the entire cohort was 8, with no difference between the groups ($P = .3$). They also had more positive lymph nodes and higher margin-positive resections, consistent with treatment-selection bias. To account for this treatment-selection bias, PSM was performed as described above, resulting in well-balanced cohorts (Table 1). Standardized mean differences were calculated for each variable and ranged between 0.01 and 0.05, indicating good balance.

Association of Adjuvant RT With Survival

For the overall cohort, the median survival rate was 32 months, and the 5-year survival rate was 30%. In the unmatched cohort, the survival rate of patients receiving adjuvant RT was similar to those under noRT (median, 28 vs 29 months; 5-year: 28% vs 29%; $P = 1.0$; Fig. 1A). In the matched cohort, patients receiving adjuvant RT had a significant survival advantage (median, 29 vs 27 months; 5-year: 28% vs 25%; $P = .017$; Fig. 1B). In the PSM multivariable analysis, factors associated with adverse survival included older age, higher comorbidity score, advanced tumors, N+ tumors, and positive margin status (Table 3). Patients receiving adjuvant RT had improved survival after PSM and multivariable adjustment (HR, 0.86; 95% CI, 0.79-0.94; $P = .001$; Table 2).

Interaction Between Adjuvant RT and Nodal Status

Further analyses were performed to further understand the impact of adjuvant RT in subgroups of nodal status. In unadjusted analysis, there were no significant differences in survival rate between adjuvant RT and noRT patients with N0 disease (median, 40 vs 40 months; $P = .6$; Supporting Fig. 2A), but the survival rate was significantly different in patients with N+ disease (median, 25 vs 23 months; $P = .03$; Supporting Fig. 2B) and in patients with Nx disease (median, 25 vs 17 months; $P = .013$; Supporting Fig. 2C). In multivariable analyses modeling the interaction between receipt of adjuvant RT and nodal status, a survival benefit again was seen for patients with N0 disease (HR, 0.76; 95% CI, 0.65-0.87; $P < .001$), N+ disease (HR, 0.78; 95% CI, 0.72-0.90; $P < .001$), and Nx disease (HR, 0.62; 95% CI, 0.68-0.79; $P < .001$; Table 3, Supporting Table 1). As a sensitivity analysis, we performed 3 separate multivariable analyses in cohorts including only those with N0, N+, and Nx disease, respectively. These analyses confirmed the benefit of adjuvant RT in both subgroups (Table 4).

Interaction Between Adjuvant RT and Margin Status

Interaction analyses were performed to further understand the impact of adjuvant RT by margin status. In unadjusted analysis, there were no significant differences in survival between adjuvant RT and noRT patients in patients with R0 resections (median, 32 vs 31 months; $P = .2$; Supporting Fig. 3A), but survival was significantly different in patients with R1 resections (median, 24 vs 20 months; $P < .001$; Supporting Fig. 3B). In multivariable analyses modeling the interaction between receipt of adjuvant RT and margin status, a survival benefit of adjuvant RT again was seen for patients with R0 (HR, 0.83; 95% CI, 0.74-0.92; $P < .001$) and R1 margin status (HR, 0.79; 95% CI, 0.66-0.93; $P < .001$; Table 3, Supporting Table 2). As a sensitivity analysis, we performed 2 separate multivariable analyses in cohorts including only those with an R0 or R1 margin, respectively. These analyses confirmed the benefit of adjuvant CT in both subgroups (Table 4).

Association of Adjuvant CT and Adjuvant RT With Survival

Interaction analyses were performed to further understand the impact of adjuvant RT by adjuvant CT status. In unadjusted analysis, there were significant differences in survival between adjuvant RT and noRT patients in patients with no adjuvant CT (noCT; median, 26 vs 23 months; $P = .02$; Fig. 2A) and in patients receiving adjuvant CT (median, 28 vs 26 months; $P = .03$; Fig. 2B). In multivariable analyses modeling the interaction between receipt of adjuvant RT and adjuvant CT status, a survival

TABLE 1. Clinicopathologic Characteristics of Distal Cholangiocarcinoma by Receipt of Adjuvant Radiotherapy in an Unmatched Cohort

		Unmatched Cohort			Matched Cohort		
		No	Yes	*P*	No	Yes	*P*
Hospital factors							
Center volume	1 (Lowest)	359 (8.6)	352 (16.3)	<.001	201 (13.3)	221 (14.6)	.3
	2	522 (12.6)	397 (18.4)		222 (14.7)	254 (16.8)	
	3	746 (18.0)	416 (19.2)		280 (18.6)	280 (18.6)	
	4	1132 (27.2)	513 (23.7)		381 (25.2)	368 (24.4)	
	5 (Highest)	1396 (33.6)	484 (22.4)		425 (28.2)	386 (25.6)	
Facility type	Community	985 (23.7)	681 (31.5)	<.001	445 (29.5)	438 (29.0)	.4
	Academic	2694 (64.8)	1120 (51.8)		875 (58.0)	855 (56.7)	
	Others	476 (11.5)	361 (16.7)		189 (12.5)	216 (14.3)	
Facility location	Northeast	1045 (25.2)	530 (24.5)	.7	388 (25.7)	370 (24.5)	.7
	South	1387 (33.4)	752 (34.8)		501 (33.2)	520 (34.5)	
	Midwest	1038 (25.0)	536 (24.8)		375 (24.9)	388 (25.7)	
	West	685 (16.5)	344 (15.9)		245 (16.2)	231 (15.3)	
Patient factors							
Year of diagnosis	2006-2007	1060 (25.5)	630 (29.1)	<.001	434 (28.8)	448 (29.7)	.3
	2008-2009	648 (15.6)	335 (15.5)		197 (13.1)	217 (14.4)	
	2010-2011	741 (17.8)	424 (19.6)		254 (16.8)	265 (17.6)	
	2012-2013	785 (18.9)	390 (18.0)		283 (18.8)	282 (18.7)	
	2014-2016	921 (22.2)	383 (17.7)		341 (22.6)	297 (19.7)	
Age at diagnosis, y	36-50	295 (7.1)	237 (11.0)	<.001	142 (9.4)	137 (9.1)	.9
	51-65	1373 (33.0)	901 (41.7)		593 (39.3)	615 (40.8)	
	66-80	2104 (50.6)	935 (43.2)		704 (46.7)	685 (45.4)	
	>80	378 (9.1)	89 (4.1)		70 (4.6)	72 (4.8)	
Sex	Male	2570 (61.9)	1376 (63.6)	.1	928 (61.5)	945 (62.6)	.5
	Female	1585 (38.1)	786 (36.4)		581 (38.5)	564 (37.4)	
CDCC score	0-1	3852 (92.7)	2061 (95.3)	<.001	1428 (94.6)	1430 (94.8)	.9
	≥2	303 (7.3)	101 (4.7)		81 (5.4)	79 (5.2)	
Insurance status	Uninsured	247 (5.9)	128 (5.9)	<.001	95 (6.3)	94 (6.2)	1.0
	Private insurance	1469 (35.4)	989 (45.7)		630 (41.7)	639 (42.3)	
	Medicaid	188 (4.5)	99 (4.6)		74 (4.9)	73 (4.8)	
	Medicare	2251 (54.2)	946 (43.8)		710 (47.1)	703 (46.6)	
Median household income	≤$47,999	1529 (36.8)	753 (34.8)	.3	547 (36.2)	525 (34.8)	.7
	$48,000-$62,999	1126 (27.1)	606 (28.0)		402 (26.6)	416 (27.6)	
	≥$63,000	1500 (36.1)	803 (37.1)		560 (37.1)	568 (37.6)	
Tumor factors							
Tumor grade	Well	506 (12.2)	261 (12.1)	.001	168 (11.1)	157 (10.4)	.8
	Moderate	1861 (44.8)	1030 (47.6)		714 (47.3)	715 (47.4)	
	Poor	1235 (29.7)	655 (30.3)		458 (30.4)	479 (31.7)	
	Anaplastic	553 (13.3)	216 (10.0)		169 (11.2)	158 (10.5)	
AJCC pathological tumor (pT) classification	pTx	939 (22.6)	463 (21.4)	<.001	302 (20.0)	320 (21.2)	.8
	pT1	454 (10.9)	106 (4.9)		92 (6.1)	82 (5.4)	
	pT2	994 (23.9)	578 (26.7)		355 (23.5)	363 (24.1)	
	pT3	1571 (37.8)	884 (40.9)		669 (44.3)	652 (43.2)	
	pT4	197 (4.7)	131 (6.1)		91 (6.0)	92 (6.1)	
AJCC pathological node (N) classification	N0	2070 (49.8)	850 (39.3)	<.001	602 (39.9)	585 (38.8)	.8
	N+	1632 (39.3)	1124 (52.0)		772 (51.2)	782 (51.8)	
	Nx	453 (10.9)	188 (8.7)		135 (8.9)	142 (9.4)	
Margin status	Negative	3302 (79.5)	1352 (62.5)	<.001	1065 (70.6)	1034 (68.5)	.2
	Positive	853 (20.5)	810 (37.5)		444 (29.4)	475 (31.5)	
Lymphovascular invasion	Absent	3305 (79.5)	1677 (77.6)	.1	1144 (75.8)	1172 (77.7)	.2
	Present	850 (20.5)	485 (22.4)		365 (24.2)	337 (22.3)	
Adjuvant chemotherapy	No	2990 (72.0)	440 (20.4)	<.001	429 (28.4)	429 (28.4)	1.0
	Yes	1165 (28.0)	1722 (79.6)		1080 (71.6)	1080 (71.6)	

Abbreviations: AJCC, American Joint Commission on Cancer; CDCC, Charlson-Deyo comorbid condition; N+, node-positive; N0, node-negative; Nx, unknown node status.
Additional variables included into the propensity matching omitted from tables were hospital factors (hospital distance) and patient factors (race, residence, education level).

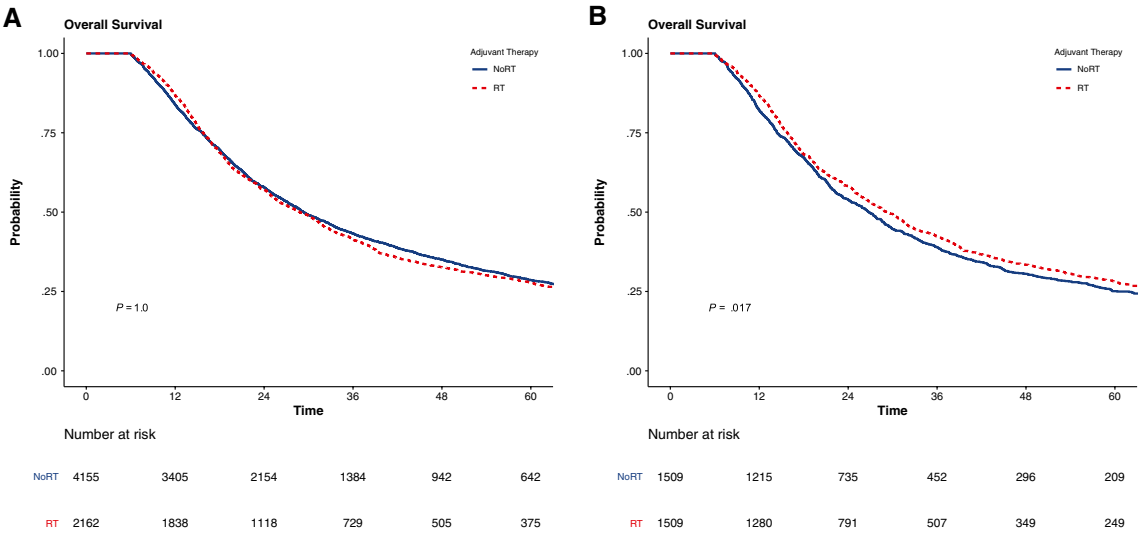

Figure 1. Overall survival of adjuvant radiotherapy following resection for distal cholangiocarcinoma in unmatched and matched cohorts. NoRT indicates no adjuvant radiotherapy; RT, adjuvant radiotherapy.

benefit of adjuvant RT again was seen for patients with noCT (HR, 0.57; 95% CI, 0.49-0.65; $P < .001$) and in patients receiving adjuvant CT (HR, 0.58; 95% CI, 0.51-0.67; $P < .001$; Table 3, Supporting Table 3). As a sensitivity analysis, we performed 2 separate multivariable analyses in cohorts including only those without or with adjuvant CT, respectively. These analyses confirmed the benefit of adjuvant CT in both subgroups (Table 4).

Sensitivity Analysis of ≥6 Lymph Nodes Examined

In this cohort, 3852 of 6317 patients (61%) had ≥6 lymph nodes examined. Of these patients, 1271 (33%) received adjuvant RT and 2581 (67%) had noRT. In the unmatched cohort, the survival rate of patients receiving adjuvant RT was similar to those receiving noRT (median, 31 vs 30 months; 5-year: 30% vs 29%; $P = .7$; Supporting Fig. 4A). In the matched cohort, patients receiving adjuvant RT had a similar survival rate (median, 31 vs 28 months, 5-year: 28% vs 26%, $P = .1$; Supporting Fig. 4B). Patients receiving adjuvant RT had improved survival after PSM and multivariable adjustment (HR, 0.88; 95% CI, 0.78-0.98; $P = .026$; Supporting Table 4). Interaction analyses performed by nodal and margin status demonstrated benefit of adjuvant RT in patients with margin-positive disease only.

DISCUSSION

Distal CCA remains a relatively uncommon malignancy without broadly accepted protocols for optimal multimodality management following curative-intent resection. Despite current National Comprehensive Cancer Network guidelines[30] that advocate adjuvant CT for all patients with dCCA, there remains an ongoing dilemma regarding the role of adjuvant RT after resection of dCCA, and practice varies significantly (Supporting Fig. 1). In this large national registry analysis including 8233 patients, adjuvant RT after resected dCCA was associated with improved survival after multivariable adjustment and accounting for treatment-selection bias. Subset analyses revealed that this benefit was maintained irrespective of pathological nodal and margin status. Although the absolute magnitude of the survival difference (2 months) is modest, it is noteworthy to point out that the survival differences in several landmark clinical trials in pancreatic cancer were also <6 months, including CONKO-001 (Charité Onkologie 001; 2.6 months), ESPAC-1 (European Study Group for Pancreatic Cancer 1; 14.6 months), and JSAP-2 (Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer 2; 3.9 months). These data suggest the routine use of adjuvant RT for dCCA is beneficial, even in the absence of nodal involvement or compromised surgical margins.

To date, there are no prospective RCTs that establish the benefit of adjuvant RT in patients with completely resected dCCA. This is because previous RCTs[9,10,17-22] included biliary tract cancers and no specific analyses by dCCA. For instance, the phase II SWOG (Southwest Oncology Group) S0809[31] demonstrated that the

TABLE 2. Multivariable Cox Regression Model of Survival of Patients With Resected Distal Cholangiocarcinoma in the Matched Cohort

		HR (95% CI)	*P*
Hospital factors			
Center volume	1 (Lowest)	Ref	.8
	2	0.96 (0.82-1.13)	
	3	0.97 (0.83-1.14)	
	4	0.87 (0.73-1.03)	
	5 (Highest)	0.87 (0.72-1.04)	
Facility type	Community	Ref	.9
	Academic	0.97 (0.85-1.10)	
	Others	1.04 (0.90-1.21)	
Facility location	Northeast	Ref	.1
	South	1.13 (1.00-1.28)	
	Midwest	1.17 (1.03-1.33)	
	West	1.14 (0.99-1.32)	
Patient factors		Ref	
Year of diagnosis	2006-2007	Ref	.3
	2008-2009	1.12 (0.96-1.30)	
	2010-2011	0.83 (0.71-0.97)	
	2012-2013	0.79 (0.67-0.93)	
	2014-2016	0.72 (0.60-0.86)	
Age at diagnosis, y	36-50	Ref	<.001
	51-65	1.09 (0.93-1.29)	
	66-80	1.24 (1.03-1.49)	
	>80	1.72 (1.33-2.22)	
Sex	Male	Ref	.9
	Female	1.02 (0.94-1.12)	
CDCC score	0-1	Ref	.1
	≥2	1.16 (0.96-1.40)	
Insurance status	Uninsured	Ref	.1
	Private Insurance	1.02 (0.84-1.24)	
	Medicaid	1.14 (0.87-1.50)	
	Medicare	1.05 (0.85-1.28)	
Median household income	≤$47,999	Ref	.05
	$48,000-$62,999	0.93 (0.83-1.06)	
	≥$63,000	0.97 (0.84-1.12)	
Tumor factors		Ref	
Tumor grade	Well	Ref	<.001
	Moderate	1.22 (1.05-1.42)	
	Poor	1.36 (1.16-1.59)	
	Anaplastic	1.38 (1.14-1.67)	
AJCC pathological tumor (T) stage	Tx	Ref	<.001
	T1	0.74 (0.59-0.93)	
	T2	1.06 (0.93-1.22)	
	T3	1.12 (0.99-1.27)	
	T4	1.17 (0.96-1.41)	
AJCC pathological node (N) stage	N0	Ref	<.001
	N+	1.58 (1.44-1.75)	
	Nx	1.64 (1.40-1.93)	
Margin status	Negative	Ref	<.001
	Positive	1.58 (1.43-1.73)	
Lymphovascular invasion	Absent	Ref	.015
	Present	1.18 (1.03-1.34)	
Adjuvant chemotherapy	No	Ref	.9
	Yes	0.99 (0.87-1.13)	
Adjuvant radiotherapy	No	Ref	.001
	Yes	0.86 (0.79-0.94)	

Abbreviations: AJCC, American Joint Commission on Cancer; CDCC, Charlson-Deyo comorbid condition; HR, hazard ratio; N+, node-positive; N0, node-negative; Nx, unknown node status; Ref, reference.
Additional variables included into the propensity matching omitted from tables were hospital factors (hospital distance) and patient factors (race, residence, education level).

TABLE 3. Multivariable Cox Regression Model of Survival of Patients With Resected Distal Cholangiocarcinoma in a Matched Cohort, With Interactions Between Radiotherapy and Nodal Status and Margin Status

		HR (95% CI)	*P*
Interaction by nodal status			
Adjuvant RT * AJCC pathological node (N) stage	N0 * noRT	Ref	<.001
	N0 * RT	0.76 (0.65-0.87)	
	N+ * noRT	1.48 (1.30-1.69)	
	N+ * RT	0.78 (0.72-0.90)	
	Nx * noRT	1.79 (1.46-2.19)	
	Nx * RT	0.62 (0.68-0.79)	
Interaction by margin status			
Adjuvant RT * margin status	R0 * noRT	Ref	<.001
	R0 * RT	0.83 (0.74-0.92)	
	R1 * noRT	1.81 (1.60-2.04)	
	R1 * RT	0.79 (0.66-0.93)	
Interaction by chemotherapy status			
Adjuvant RT * adjuvant CT	noRT * noCT	Ref	<.001
	RT * noCT	0.57 (0.49-0.65)	
	noRT * CT	0.67 (0.58-0.77)	
	RT * CT	0.58 (0.51-0.67)	

Abbreviations: AJCC, American Joint Commission on Cancer; CT, chemotherapy; N+, node-positive; N0, node-negative; noCT, no adjuvant chemotherapy; noRT, no adjuvant radiotherapy; Nx, unknown node status; Ref, reference; RT, radiotherapy.

TABLE 4. Association of Adjuvant Radiotherapy With Overall Survival of Patients With Resected Distal Cholangiocarcinoma in Unmatched and Matched Cohorts and Stratified by Nodal Status and Margin Status

Cohort	Adjuvant RT	Median Survival (IQR), mo	HR (95% CI)	*P*
Stratified by nodal status in matched cohort				
N0	noRT	39.5 (33.3-45.0)	Ref	.042
	RT	40.2 (36.6-45.5)	0.87 (0.76-0.99)	
N+	noRT	22.6 (21.4-25.1)	Ref	.021
	RT	24.5 (22.3-27.0)	0.87 (0.77-0.98)	
Nx	noRT	16.5 (14.4-23.3)	Ref	.003
	RT	24.8 (20.3-31.5)	0.64 (0.48-0.86)	
Stratified by margin status in matched cohort				
R0	noRT	31.4 (28.9-34.0)	Ref	.042
	RT	32.1 (30.5-36.0)	0.90 (0.81-0.99)	
R1	noRT	19.6 (18.1-20.9)	Ref	.002
	RT	23.5 (20.4-25.8)	0.78 (0.67-0.91)	
Stratified by receipt of CT in matched cohort				
noRT	noCT	25.2 (21.6-28.9)	Ref	.004
	CT	26.1 (23.8-30.7)	0.79 (0.68-0.93)	
RT	noCT	27.4 (25.5-28.9)	Ref	.049
	CT	30.2 (28.2-32.1)	0.90 (0.81-1.00)	

Abbreviations: CT, Adjuvant chemotherapy; HR, hazard ratio; IQR, interquartile range; noCT, no adjuvant chemotherapy; noRT, no adjuvant radiotherapy; Ref, reference; RT, adjuvant radiotherapy.

combination of gemcitabine, capecitabine, and concurrent capecitabine with adjuvant RT was well-tolerated. Although the ongoing phase III SWOG S0809 will

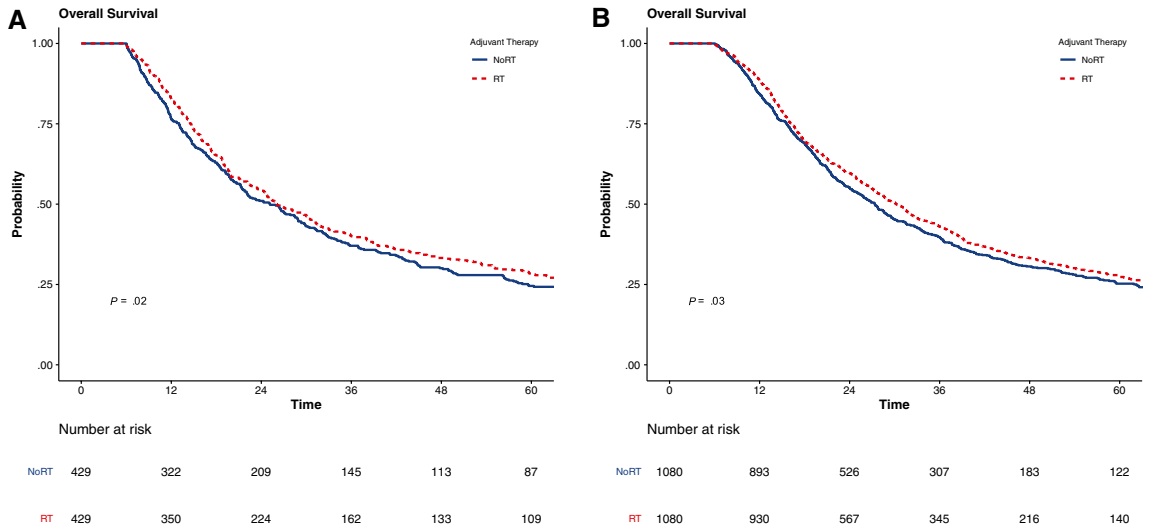

Figure 2. Overall survival of adjuvant radiotherapy following resection for distal cholangiocarcinoma stratified by adjuvant chemotherapy in matched cohorts. (A) No adjuvant chemotherapy. (B) Adjuvant chemotherapy. NoRT indicates no adjuvant radiotherapy; RT, adjuvant radiotherapy.

improve the current evidence base, the inclusion of gallbladder carcinoma may similarly complicate the interpretation of results for dCCA. Therefore, current evidence for adjuvant RT in resected dCCA is limited to retrospective studies, offering conflicting results.[13-16] A surveillance, epidemiology, and end results analysis demonstrated significant survival benefit with adjuvant RT compared with noRT for stage I/II disease (36.0 vs 28.0 months; $P < .001$), not stage III (including nodal involvement) disease.[13] Previous analyses utilizing the NCDB failed to show any benefit with the addition of adjuvant RT to adjuvant CT (n = 411) compared with adjuvant CT (n = 260; median, 32.1 vs 34.5 months) for resected dCCA.[14] These findings may reflect type II errors based on insufficient power. In the present large study, though still retrospective, robust methods were used to account for treatment selection bias and survival benefit was still found with adjuvant RT, irrespective of the receipt of adjuvant CT.

The presence of high-risk factors, such as nodal involvement or positive margins, is commonly used to select patients for adjuvant therapy, as evidenced by the distribution of adjuvant RT use in the unmatched cohort. To date, no published studies have explored the role of adjuvant RT specifically in patients with node-negative disease or margin-negative resections. Anecdotally, these patients are likely to have better survival outcomes and do not routinely receive adjuvant treatment. However, local and systemic recurrence in these patients may be as high as 20%[32-35] and 40%,[32,34,36,37] respectively. Further, risk of nodal understaging from low lymph nodes examined may also be an issue, owing to varying practices within institutions. For instance, in the present study, only 3852 of 6317 patients (61%) had ≥6 lymph nodes examined. In addition, our results suggest that patients with Nx disease have poorer survival rates than those with N1 disease. Therefore, adjuvant RT has a role in these subgroups of patients by reducing or delaying recurrence and prolonging survival, as these are high-risk patients. However, there may be a subgroup of patients in whom the benefit of adjuvant RT does not outweigh the risk,[38] but these patients have not yet been defined.

Several limitations of our study should be acknowledged. First, despite the use of PSM to address treatment selection bias, the potential for residual bias remains in this retrospective cohort study. Second, the duration of adjuvant CT and the specific regimens used are not available from NCDB. As a result, we were not able to assess the role of adjuvant RT-sensitizing CT, which may or may not be associated with a similar survival benefit. Third, we did not assess the role of neoadjuvant RT, which may or may not be associated with a similar survival benefit. Fourth, patients with survival of <6 months were excluded primarily to account for patients who did not survive long enough to receive adjuvant RT. However, it is possible that doing so also excluded patients who died because of adjuvant RT-related complications, although this is likely to be a small group. Finally, because NCDB does not include data on recurrence patterns, we can only

speculate as to whether improved survival was associated with local or systemic disease control.

In conclusion, in this large nationwide retrospective study, adjuvant RT was associated with a survival benefit in patients with resected dCCA, regardless of pathological nodal involvement, resection margin status, and receipt of adjuvant CT. These data suggest adjuvant RT should be broadly considered in the multimodality treatment of dCCA. Broad acceptance of the routine use of adjuvant RT in dCCA would also support its use in the neoadjuvant setting, just as in pancreatic cancer, so that postoperative complications have less impact on the completion of multimodality therapy.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Sivesh K. Kamarajah: Formal analysis, investigation, methodology, supervision, writing–original draft, and writing–review and editing. **Filip Bednar:** Investigation, methodology, and writing–review and editing. **Clifford S. Cho:** Investigation, methodology, and writing–review and editing. **Hari Nathan:** Conceptualization, data curation, formal analysis, investigation, methodology, supervision, writing original draft, and writing–review and editing.

REFERENCES

1. Andrianello S, Paiella S, Allegrini V, et al. Pancreaticoduodenectomy for distal cholangiocarcinoma: surgical results, prognostic factors, and long-term follow-up. *Langenbecks Arch Surg*. 2015;400:623-628. doi:10.1007/s00423-015-1320-0
2. Koo TR, Eom KY, Kim IA, et al. Patterns of failure and prognostic factors in resected extrahepatic bile duct cancer: implication for adjuvant radiotherapy. *Radiat Oncol J*. 2014;32:63-69. doi:10.3857/roj.2014.32.2.63
3. van der Gaag NA, Kloek JJ, de Bakker JK, et al. Survival analysis and prognostic nomogram for patients undergoing resection of extrahepatic cholangiocarcinoma. *Ann Oncol*. 2012;23:2642-2649. doi:10.1093/annonc/mds077
4. Kim HJ, Kim CY, Hur YH, et al. Prognostic factors for survival after curative resection of distal cholangiocarcinoma: perineural invasion and lymphovascular invasion. *Surg Today*. 2014;44:1879-1886. doi:10.1007/s00595-014-0846-z
5. Kiriyama M, Ebata T, Aoba T, et al. Prognostic impact of lymph node metastasis in distal cholangiocarcinoma. *Br J Surg*. 2015;102:399-406. doi:10.1002/bjs.9752
6. Kamarajah SK, Burns WR, Frankel TL, Cho CS, Nathan H. Validation of the American Joint Commission on Cancer (AJCC) 8th Edition Staging System for Patients with Pancreatic Adenocarcinoma: a surveillance, epidemiology and end results (SEER) analysis. *Ann Surg Oncol*. 2017;24:2023-2030. doi:10.1245/s10434-017-5810-x
7. Jang JY, Kim SW, Park DJ, et al. Actual long-term outcome of extrahepatic bile duct cancer after surgical resection. *Ann Surg*. 2005;241:77-84. doi:10.1097/01.sla.0000150166.94732.88
8. Yamamoto M, Takasaki K, Otsubo T, Katsuragawa H, Katagiri S. Recurrence after surgical resection of intrahepatic cholangiocarcinoma. *J Hepatobiliary Pancreat Surg*. 2001;8:154-157. doi:10.1007/s005340170039
9. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol*. 2019;20:663-673. doi:10.1016/S1470-2045(18)30915-X
10. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg*. 1999;230:776-782; discussion 782-784.
11. Kamarajah SK, Sonnenday CJ, Cho CS, et al. Association of adjuvant radiotherapy with survival after margin-negative resection of pancreatic ductal adenocarcinoma: a propensity-matched National Cancer Database (NCDB) analysis. *Ann Surg*. 2019. doi:10.1097/SLA.0000000000003242. Online ahead of print.
12. Versteijne E, Suker M, Groothuis K, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. *J Clin Oncol*. 2020;38:1763-1773. doi:10.1200/JCO.19.02274
13. Vern-Gross TZ, Shivnani AT, Chen K, et al. Survival outcomes in resected extrahepatic cholangiocarcinoma: effect of adjuvant radiotherapy in a surveillance, epidemiology, and end results analysis. *Int J Radiat Oncol Biol Phys*. 2011;81:189-198. doi:10.1016/j.ijrobp.2010.05.001
14. Ecker BL, Vining CC, Roses RE, et al. Identification of patients for adjuvant therapy after resection of carcinoma of the extrahepatic bile ducts: a propensity score-matched analysis. *Ann Surg Oncol*. 2017;24:3926-3933. doi:10.1245/s10434-017-6095-9
15. Hughes MA, Frassica DA, Yeo CJ, et al. Adjuvant concurrent chemoradiation for adenocarcinoma of the distal common bile duct. *Int J Radiat Oncol Biol Phys*. 2007;68:178-182. doi:10.1016/j.ijrobp.2006.11.048
16. Nelson JW, Ghafoori AP, Willett CG, et al. Concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys*. 2009;73:148-153. doi:10.1016/j.ijrobp.2008.07.008
17. 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;95:1685-1695. doi:10.1002/cncr.10831
18. Ebata T, Hirano S, Konishi M, et al. Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. *Br J Surg*. 2018;105:192-202. doi:10.1002/bjs.10776
19. Morak MJM, van der Gaast A, Incrocci L, et al. Adjuvant intra-arterial chemotherapy and radiotherapy versus surgery alone in resectable pancreatic and periampullary cancer. *Ann Surg*. 2008;248:1031-1041. doi:10.1097/sla.0b013e318190c53e
20. 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;308:147-156. doi:10.1001/jama.2012.7352
21. Smeenk HG, van Eijck CH, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. *Ann Surg*. 2007;246:734-740. doi:10.1097/SLA.0b013e318156eef3
22. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350:1200-1210. doi:10.1056/NEnglJMedoa032295
23. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol*. 2012;30:1934-1940. doi:10.1200/JCO.2011.40.5381
24. Ghidini M, Tomasello G, Botticelli A, et al. Adjuvant chemotherapy for resected biliary tract cancers: a systematic review and meta-analysis. *HPB (Oxford)*. 2017;19:741-748. doi:10.1016/j.hpb.2017.05.010
25. Rangarajan K, Simmons G, Manas D, Malik H, Hamady ZZ. Systemic adjuvant chemotherapy for cholangiocarcinoma surgery: a systematic review and meta-analysis. *Eur J Surg Oncol*. 2020;46(4 pt A):684-693. doi:10.1016/j.ejso.2019.11.499

26. Bilimoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. *Cancer*. 2007;110:738-744. doi:10.1002/cncr.22852
27. Merkow RP, Rademaker AW, Bilimoria KY. Practical guide to surgical data sets: National Cancer Database (NCDB). *JAMA Surg*. 2018;153:850-851. doi:10.1001/jamasurg.2018.0492
28. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. *J Clin Oncol*. 2013;31:2963-2969. doi:10.1200/JCO.2013.49.5283
29. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med*. 2014;33:1242-1258. doi:10.1002/sim.5984
30. Benson AB, D'Angelica MI, Abbott DE, et al. Guidelines insights: hepatobiliary cancers, version 2.2019. *J Natl Compr Canc Netw*. 2019;17:302-310. doi:10.6004/jnccn.2019.0019
31. Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: a phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. *J Clin Oncol*. 2015;33:2617-2622. doi:10.1200/JCO.2014.60.2219
32. Woo SM, Ryu JK, Lee SH, et al. Recurrence and prognostic factors of ampullary carcinoma after radical resection: comparison with distal extrahepatic cholangiocarcinoma. *Ann Surg Oncol*. 2007;14:3195-3201. doi:10.1245/s10434-007-9537-y
33. Courtin-Tanguy L, Rayar M, Bergeat D, et al. The true prognosis of resected distal cholangiocarcinoma. *J Surg Oncol*. 2016;113:575-580. doi:10.1002/jso.24165
34. Komaya K, Ebata T, Shirai K, et al. Recurrence after resection with curative intent for distal cholangiocarcinoma. *Br J Surg*. 2017;104:426-433. doi:10.1002/bjs.10452
35. Kurosaki I, Hatakeyama K, Minagawa M, Sato D. Portal vein resection in surgery for cancer of biliary tract and pancreas: special reference to the relationship between the surgical outcome and site of primary tumor. *J Gastrointest Surg*. 2008;12:907-918. doi:10.1007/s11605-007-0387-5
36. Kim BH, Kim K, Chie EK, et al. Long-term outcome of distal cholangiocarcinoma after pancreaticoduodenectomy followed by adjuvant chemoradiotherapy: a 15-year experience in a single institution. *Cancer Res Treat*. 2017;49:473-483. doi:10.4143/crt.2016.166
37. Maeta T, Ebata T, Hayashi E, et al. Pancreatoduodenectomy with portal vein resection for distal cholangiocarcinoma. *Br J Surg*. 2017;104:1549-1557. doi:10.1002/bjs.10596
38. Moekotte AL, Lof S, Van Roessel S, et al. Histopathologic predictors of survival and recurrence in resected ampullary adenocarcinoma: international multicenter cohort study. *Ann Surg*. 2020;272:1086-1093. doi:10.1097/SLA.0000000000003177