DR. SIVESH KATHIR KAMARAJAH (Orcid ID : 0000-0002-2748-0011)

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Survival Benefit with Adjuvant Radiotherapy after Resection of Distal Cholangiocarcinoma: A Propensity Matched National Cancer Database (NCDB) Analysis

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

1. Department of HPB and Transplant Surgery, The 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, University of Michigan, Ann Arbor, MI, USA

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

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Abstract

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. We aimed to evaluate the association of RT on survival after surgical resection of dCCA compared to no RT (noRT).

Methods

Using National Cancer Database (NCDB) data from 2004 to 2016, we identified patients undergoing pancreatoduodenectomy for non-metastatic dCCA. Patients with neoadjuvant radiotherapy and chemotherapy and survival <6 mo1nths 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 RT with survival.

Results

Of 2,162 (34%) RT and 4,155 (66%) noRT patients, 1,509 RT and 1,509 noRT patients remained in the cohort after matching. The rates of node-negative (N0), node-positive disease (N+), and unknown node status (Nx) were 39%, 51%, and 10%, respectively. After matching, RT was associated with improved survival (median 29.3 vs 26.8 months, p<0.001), which remained after multivariable adjustment (HR 0.86, $CI_{95\%}$: 0.80 - 0.93, p<0.001). Multivariable interaction analyses showed this benefit was seen irrespective of nodal status (N0: HR 0.77, $CI_{95\%}$: 0.66 - 0.89, p<0.001; N+: HR 0.79, $CI_{95\%}$: 0.71 - 0.89, p<0.001) and margin status (R0: HR 0.58, $CI_{95\%}$: 0.50 - 0.67, p<0.001; R1: HR 0.87, $CI_{95\%}$: 0.78 - 0.96, p=0.007). Stratified analyses by nodal and margin status demonstrated consistent results.

Conclusion

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

Word Count: 260

Keywords: radiotherapy, distal cholangiocarcinoma, resection, survival, chemotherapy

Precis: RT after dCCA resection was associated with a survival benefit in patients, even in patients with margin- or node-negative resections. RT should be considered routinely irrespective of margin and nodal status after resection for dCCA.

Introduction

Despite advances in multimodal treatment, distal cholangiocarcinoma (dCCA) has poor 5-year survival rates ranging from 20% - 50%, even after resection.[1-6] Because local recurrence rates may be as high as 50%,[7, 8] incorporation of chemotherapy has been the focus of study, and a recent randomized controlled trial has demonstrated a survival benefit with adjuvant systemic chemotherapy.[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] suggesting some survival benefit of RT, the role of RT in biliary tract malignancy remains unclear.

To date, high-quality evidence on RT for dCCA is lacking. Firstly, the rarity of dCCA means recruitment to RCTs is difficult, and no single RCT focused on RT in dCCA exists. Secondly, current evidence limited to retrospective single-center, multi-institutional series offer conflicting evidence regarding the benefit of RT.[13-16] As a result, current clinical practice is guided by evidence from randomized controlled trials (RCTs)[9, 10, 17-22] and meta-analyses[23-25] drawn from biliary tract cancers (BTC) are conflicting. Because different BTC subtypes (i.e., intrahepatic, hilar, and distal) have varying prognoses, genetic profiles, and possibly responses to RT, findings from subgroup analyses for dCCA within these RCTs are often underpowered. Therefore, the use of 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.

We sought to add evidence to this debate by performing a large, nationwide, high-quality retrospective study to assess the potential benefit of RT after resection of dCCA. With contemporary data from the National Cancer Data Base (NCDB), we analyzed the association of 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, and we also assessed survival in clinically relevant subgroups of patients based on nodal and margin status.

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 1,500 CoC-accredited hospitals and includes >70 % of all newly diagnosed malignancies in the USA. It contains specific details about patient demographics (age, sex, race, payer), facility type and location, tumor characteristics (size, grade, stage, histology), treatment course (type of surgery, receipt of chemotherapy, and radiation therapy), 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 non-metastatic dCCA undergoing pancreatoduodenectomy between 2004 and 2016. International Classification of Disease for Oncology, Third Edition (ICD-O-3), classification was used to select adenocarcinoma histology and exclude mucinous tumors, neuroendocrine tumors, and other histologies. Patients with other concomitant cancer diagnoses, those where dCCA were not their first cancer, those who received neoadjuvant chemotherapy or radiotherapy, those with missing data on lymph node status were excluded. In addition, patients with a 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 NCDB: age (36 - 50, 51 - 65, 66 - 80, >80), race (white, black, other), Charlson/Deyo 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 (Midwest, Northeast, South, 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, N+, Nx), tumor grade/differentiation (well/moderate, poor/anaplastic, unknown), lymphovascular invasion (absent, present) and margin status (positive, negative).

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

Statistical Analysis

Categorical variables were compared using the chi-squared test. Non-normally 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 RT, i.e., 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 standard deviations).[29] Balance diagnostics were conducted by using standardized mean differences, with a value <0.1 indicating good balance.[29] We then evaluated overall survival (OS) of matched patients with and without adjuvant chemotherapy. In order 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 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 <0.05 was considered to be statistically significant. Data analysis was performed using R Foundation Statistical software (R 3.2.2) with TableOne, ggplot2, Hmisc, Matchit and survival packages (R Foundation for Statistical Computing, Vienna, Austria) 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 6,317 patients with surgically resected dCCA. Of these patients, 2,162 (34%) received RT and 4,155 (66%) had noRT. Median follow-up was 19 months (interquartile range 10 - 33 months). Baseline demographics of the unmatched cohort confirmed that patients receiving RT were younger and had lower comorbidity burden (Table 1). There was also a variation in the receipt of RT between centres from 0% to 100% (Supplementary Figure 1). The median number of lymph nodes examined in the entire cohort was 8, with no difference between the groups (p = 0.3). 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. This resulted 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 Radiotherapy with Survival

For the overall cohort, median survival was 32 months, and 5-year survival was 30%. In the unmatched cohort, the survival of patients receiving RT was similar to those under noRT (median: 28 vs 29 months, 5-year: 28% vs 29%, p=1.0) (Figure 1A). In the matched cohort, patients receiving RT had a significant survival advantage (median: 29 vs 27 months, 5-year: 28% vs 25%, p=0.017) (Figure 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 RT had improved survival after PSM and multivariable adjustment (HR: 0.86, $CI_{95\%}$: 0.79 - 0.94, p=0.001) (Table 2).

Interaction between Adjuvant Radiotherapy and Nodal Status

Further analyses were performed to further understand the impact of RT in subgroups of nodal status. In unadjusted analysis, there were no significant differences in survival between RT and noRT patients in patients with N0 disease (median: 40 vs 40 months, p=0.6) (Supplementary Figure 2A), but were significantly different in patients with N+

disease (median: 25 vs 23 months, p=0.03) (Supplementary Figure 2B) and in patients with Nx disease (median: 25 vs 17 months, p=0.013) (Supplementary Figure 2C). In multivariable analyses modeling the interaction between receipt of RT and nodal status, a survival benefit again was seen for patients with N0 disease (HR: 0.76, $CI_{95\%}$: 0.65 - 0.87, p<0.001), N+ disease (HR: 0.78, $CI_{95\%}$: 0.72 - 0.90, p<0.001), and Nx disease (HR: 0.62, $CI_{95\%}$: 0.68 - 0.79, p<0.001) (Table 3, Supplementary Table 1). As a sensitivity analysis, we performed three separate multivariable analyses in cohorts including only those with N0, N+ and Nx disease, respectively. These analyses confirmed the benefit of RT in both subgroups (Table 4).

Interaction between Adjuvant Radiotherapy and Margin Status

Interaction analyses were performed to further understand the impact of RT by margin status. In unadjusted analysis, there were no significant differences in survival between RT and noRT patients in patients with R0 resections (median: 32 vs 31 months, p=0.2) (Supplementary Figure 3A), but survival was significantly different in patients with R1 resections (median: 24 vs 20 months, p<0.001) (Supplementary Figure 3B). In multivariable analyses modeling the interaction between receipt of RT and margin status, a survival benefit of RT again was seen for patients with R0 (HR: 0.83, $CI_{95\%}$: 0.74 - 0.92, p<0.001) and R1 margin status (HR: 0.79, $CI_{95\%}$: 0.66 - 0.93, p<0.001) (Table 3, Supplementary Table 2). As a sensitivity analysis, we performed two separate multivariable analyses in cohorts including only those with R0 or R1 margin, respectively. These analyses confirmed the benefit of AC in both subgroups (Table 4).

Association of Adjuvant Chemotherapy and Radiotherapy with Survival

Interaction analyses were performed to further understand the impact of RT by AC status. In unadjusted analysis, there were significant differences in survival between RT and noRT patients in patients with no AC (median: 26 vs 23 months, p=0.02) (Figure 2A) and in patients receiving AC (median: 28 vs 26 months, p=0.03) (Figure 2B). In multivariable analyses modeling the interaction between receipt of RT and AC status, a survival benefit of RT again was seen for patients with no AC (HR: 0.57, $CI_{95\%}$: 0.49 - 0.65, p<0.001) and in patients receiving AC (HR: 0.58, $CI_{95\%}$: 0.51 - 0.67, p<0.001) (Table 3, Supplementary

Table 3). As a sensitivity analysis, we performed two separate multivariable analyses in cohorts including only those without or with AC, respectively. These analyses confirmed the benefit of AC in both subgroups (Table 4).

Sensitivity Analysis of ≥6 Lymph Nodes Examined

"In this cohort, 61.0% (3,852/6,317) of patients had ≥6 lymph nodes examined. Of these patients, 1,271 (33%) received RT and 2,581 (67%) had noRT. In the unmatched cohort, the survival of patients receiving RT was similar those under noRT (median: 31 vs 30 months, 5-year: 30% vs 29%, p=0.7) (Supplementary Figure 4A). In the matched cohort, patients receiving RT had a similar survival (median: 31 vs 28 months, 5-year: 28% vs 26%, p=0.1) (Supplementary Figure 4B). Patients receiving RT had improved survival after PSM and multivariable adjustment (HR: 0.88, $CI_{95\%}$: 0.78 - 0.98, p=0.026) (Supplementary Table 4). Interaction analyses performed by nodal and margin status demonstrated benefit of 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 NCCN guidelines[30] advocate AC for all dCCA patients, there remains an ongoing dilemma regarding the role of RT after resection of dCCA, and practice varies significantly (Supplementary Figure 1). In this large national registry analysis including 8,233 patients, 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 such as CONKO-001 (2.6 months), ESPAC-1 (4.6 months), and JSAP-2 (3.9 months).These data suggest a benefit of the routine use of RT for dCCA, even in the absence of nodal involvement or compromised surgical margins.

To date, there are no prospective RCTs that establish the benefit of RT in patients with completely resected dCCA. This is because previous RCTs[9,10,17-22] include BTC's and no specific analyses by dCCA. For instance, the phase II SWOG S0809[31] demonstrated the combination of gemcitabine, capecitabine and concurrent capecitabine with radiotherapy was well tolerated. Whilst the ongoing phase III SWOG S0809 will improve current evidence base, the inclusion of GBC may similarly complicate interpretation of results for dCCA. Therefore, current evidence for RT in resected dCCA is limited to retrospective, offering conflicting results.[13-16] A Surveillance, Epidemiology, and End Results (SEER) analysis demonstrated significant survival benefit with RT compared to noRT for Stage I/II disease (36.0 vs 28.0 months, p<0.001), not Stage III (including nodal involvement) disease.[13] Previous analyses utilizing the NCDB failed to demonstrate any benefit with addition to RT to AC (n=411) compared to AC (n=260) (median: 32.1 vs 34.5 months) for resected dCCA.[14] These findings may reflect type II errors due to insufficient power. In the present large study, while still retrospective, used robust methods to account for

treatment selection bias and still demonstrated survival benefit with RT, irrespective of the receipt of AC.

The presence of high-risk factors, such as nodal involvement or positive margins, is commonly used to select patients for adjuvant therapy, as evidence by the distribution of RT use in the unmatched cohort. To date, no published studies have explored the role of 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 61.0% (3,852/6,317) of patients had ≥6 lymph nodes examined. In addition, our results suggest that patients with Nx disease have poorer survival than those with N1 disease. Therefore, 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 RT does not outweigh the risk[38], but these 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 chemotherapy and the specific regimens used are not available from NCDB. As a result, we did not able to assess the role of RT-sensitizing chemotherapy, 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 RT. However, it is possible that doing so also excluded patients who died due to 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.

Conclusion

In this large nationwide retrospective study, RT was associated with a survival benefit in patients with resected dCCA, regardless of pathological nodal involvement, resection margin status and receipt of AC. These data suggest RT should be broadly considered in the multimodality treatment of dCCA. Broad acceptance of the routine use of 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.

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Figure Legends

Figure 1 Overall survival of adjuvant radiotherapy following resection for distal cholangiocarcinoma in unmatched and matched cohorts

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

Table 1 Clinicopathologic characteristics of distal cholangiocarcinoma by receipt of adjuvant radiotherapy in unmatched cohort

		Unmatched Cohort			Matched Cohort		
		No	Yes	p-value	No	Yes	p-value
Hospital Factors							
Center Volume	1 (Lowest)	359 (8.6)	352 (16.3)	<0.001	201 (13.3)	221 (14.6)	0.3
	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)	<0.001	445 (29.5)	438 (29.0)	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)	0.7	388 (25.7)	370 (24.5)	0.7
	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)	<0.001	434 (28.8)	448 (29.7)	0.3
	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, years	36-50	295 (7.1)	237 (11.0)	<0.001	142 (9.4)	137 (9.1)	0.9
	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)	0.1	928 (61.5)	945 (62.6)	0.5
	Female	1585 (38.1)	786 (36.4)		581 (38.5)	564 (37.4)	
CDCC Score	0-1	3852 (92.7)	2061 (95.3)	<0.001	1428 (94.6)	1430 (94.8)	0.9
	≥2	303 (7.3)	101 (4.7)		81 (5.4)	79 (5.2)	
Insurance Status	Uninsured	247 (5.9)	128 (5.9)	<0.001	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)	0.3	547 (36.2)	525 (34.8)	0.7
	$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)	0.001	168 (11.1)	157 (10.4)	0.8
	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 T Classification	pTx	939 (22.6)	463 (21.4)	<0.001	302 (20.0)	320 (21.2)	0.8
	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 N Classification	N0	2070 (49.8)	850 (39.3)	<0.001	602 (39.9)	585 (38.8)	0.8
	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)	<0.001	1065 (70.6)	1034 (68.5)	0.2
	Positive	853 (20.5)	810 (37.5)		444 (29.4)	475 (31.5)	
Lymphovascular Invasion	Absent	3305 (79.5)	1677 (77.6)	0.1	1144 (75.8)	1172 (77.7)	0.2
	Present	850 (20.5)	485 (22.4)		365 (24.2)	337 (22.3)	
Adjuvant Chemotherapy	No	2990 (72.0)	440 (20.4)	<0.001	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 Comission on Cancer, CDCC: Charlson-Deyo comorbidity. ** Additional variables included into the propensity matching omitted from tables were hospital factors (hospital distance), patient factors (race, residence, education level)*

Table 2 Multivariable Cox regression model of survival of patients with resected distal cholangiocarcinoma in the matched cohort

		Hazard ratio ($CI_{95\%}$)	p-value
Hospital Factors			
Center Volume	1 (Lowest)	REF	0.8
	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	0.9
	Academic	0.97 (0.85-1.10)	
	Others	1.04 (0.90-1.21)	
Facility Location	Northeast	REF	0.1
	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	0.3
	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, years	36 - 50	REF	<0.001
	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	0.9
	Female	1.02 (0.94-1.12)	
CDCC Score	0 - 1	REF	0.1
	≥2	1.16 (0.96-1.40)	
Insurance Status	Uninsured	REF	0.1
	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	0.05
	$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	<0.001
	Moderate	1.22 (1.05-1.42)	
	Poor	1.36 (1.16-1.59)	
	Anaplastic	1.38 (1.14-1.67)	
AJCC Pathological T Stage	Tx	REF	<0.001
	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 N Stage	N0	REF	<0.001
	N+	1.58 (1.44-1.75)	
	Nx	1.64 (1.40-1.93)	
Margin Status	Negative	REF	<0.001
	Positive	1.58 (1.43-1.73)	
Lymphovascular Invasion	Absent	REF	0.015
	Present	1.18 (1.03-1.34)	
Adjuvant Chemotherapy	No	REF	0.9
	Yes	0.99 (0.87-1.13)	
Adjuvant Radiotherapy	No	REF	0.001
	Yes	0.86 (0.79-0.94)	

**Abbreviations: AJCC: American Joint Comission on Cancer, CDCC: Charlson-Deyo comorbidity. ** Additional variables included into the propensity matching omitted from tables were hospital factors (hospital distance), patient factors (race, residence, education level)*

Table 3 Multivariable cox regression model of survival of patients with resected distal cholangiocarcinoma in matched cohort, with interactions between radiotherapy and nodal status and margin status

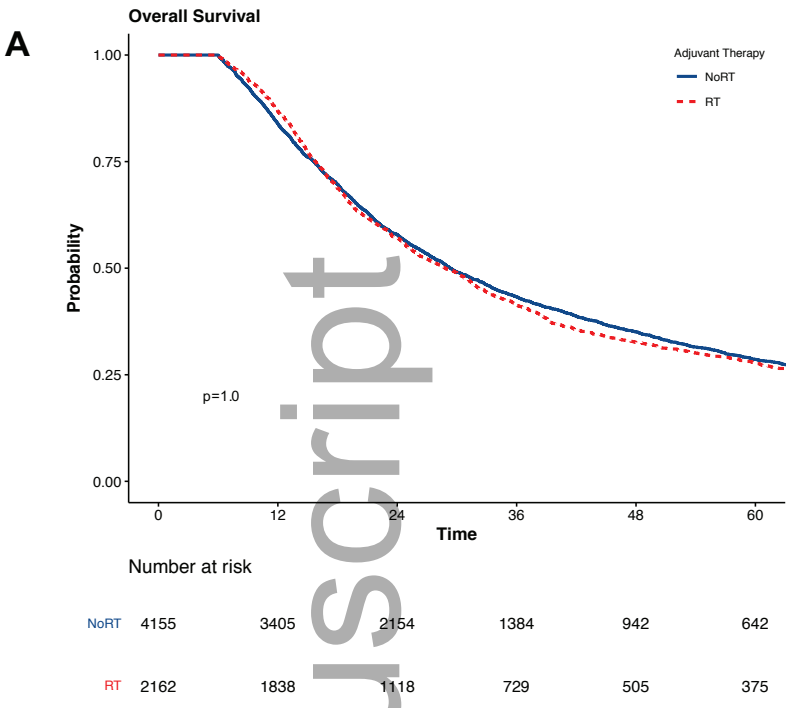
		Hazard ratio ($CI_{95\%}$)	p-value
Interaction by nodal status			
	N0 * noRT	REF	<0.001
	N0 * RT	0.76 (0.65 - 0.87)	
Adjuvant Radiotherapy * AJCC	N+ * noRT	1.48 (1.30 - 1.69)	
Pathological N Stage	N+ * RT	0.78 (0.72 - 0.90)	
	Nx * noRT	1.79 (1.46 - 2.19)	
	Nx * RT	0.62 (0.68 - 0.79)	
Interaction by margin status			
	R0 * noRT	REF	<0.001
Adjuvant Radiotherapy * Margin	R0 * RT	0.83 (0.74 - 0.92)	
Status	R1 * noRT	1.81 (1.60 - 2.04)	
	R1 * RT	0.79 (0.66 - 0.93)	
Interaction by chemotherapy status			
Adjuvant Radiotherapy * Adjuvant Chemotherapy	noRT * No AC	REF	<0.001
	RT * No AC	0.57 (0.49 - 0.65)	
	noRT * AC	0.67 (0.58 - 0.77)	
	RT * AC	0.58 (0.51 - 0.67)	

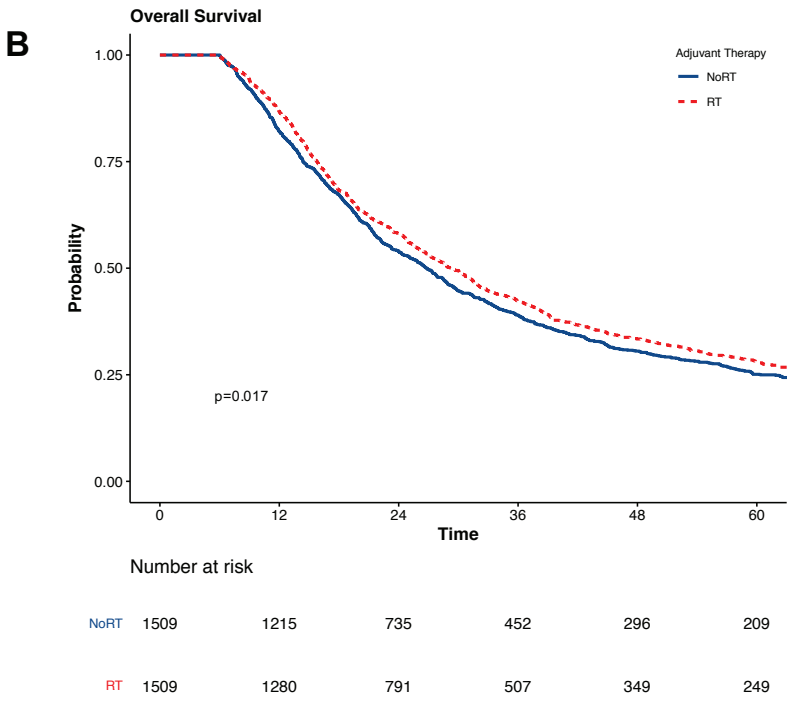
AC: Adjuvant chemotherapy, RT: Adjuvant radiotherapy, AJCC: American Joint Comission on Cancer, CDCC: Charlson Deyo Comorbidity score, noRT: No radiotherapy, REF: Reference

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	Radiotherapy	Median survival (IQR), months	Hazard ratio ($CI_{95\%}$)	p-value
Stratified by nodal status in matched cohort				
N0	noRT	39.5 (33.3 - 45.0)	REF	0.042
	RT	40.2 (36.6 - 45.5)	0.87 (0.76 - 0.99)	
N+	noRT	22.6 (21.4 - 25.1)	REF	0.021
	RT	24.5 (22.3 - 27.0)	0.87 (0.77 - 0.98)	
Nx	noRT	16.5 (14.4 - 23.3)	REF	0.003
	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	0.042
	RT	32.1 (30.5 - 36.0)	0.90 (0.81-0.99)	
R1	noRT	19.6 (18.1 - 20.9)	REF	0.002
	RT	23.5 (20.4 - 25.8)	0.78 (0.67-0.91)	
Stratified by receipt of AC in matched cohort				
noRT	noAC	25.2 (21.6 - 28.9)	REF	0.004
	AC	26.1 (23.8 - 30.7)	0.79 (0.68-0.93)	
RT	noAC	27.4 (25.5 - 28.9)	REF	0.049
	AC	30.2 (28.2 - 32.1)	0.90 (0.81-1.00)	

AC: Adjuvant chemotherapy, RT: adjuvant radiotherapy, CI: Confidence Interval, IQR: Interquartile Range, noAC: no adjuvant chemotherapy, noRT: no adjuvant radiotherapy, REF: reference





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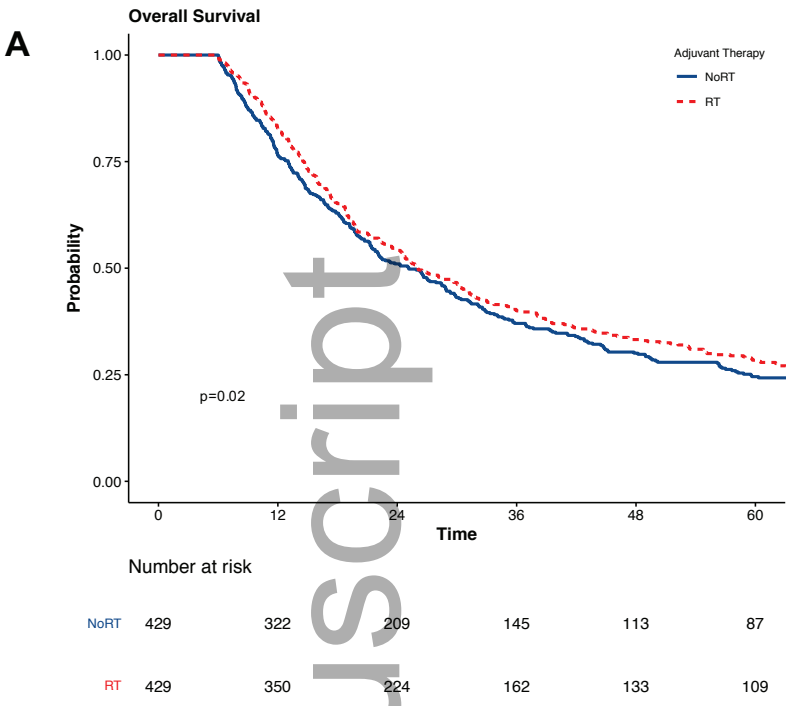

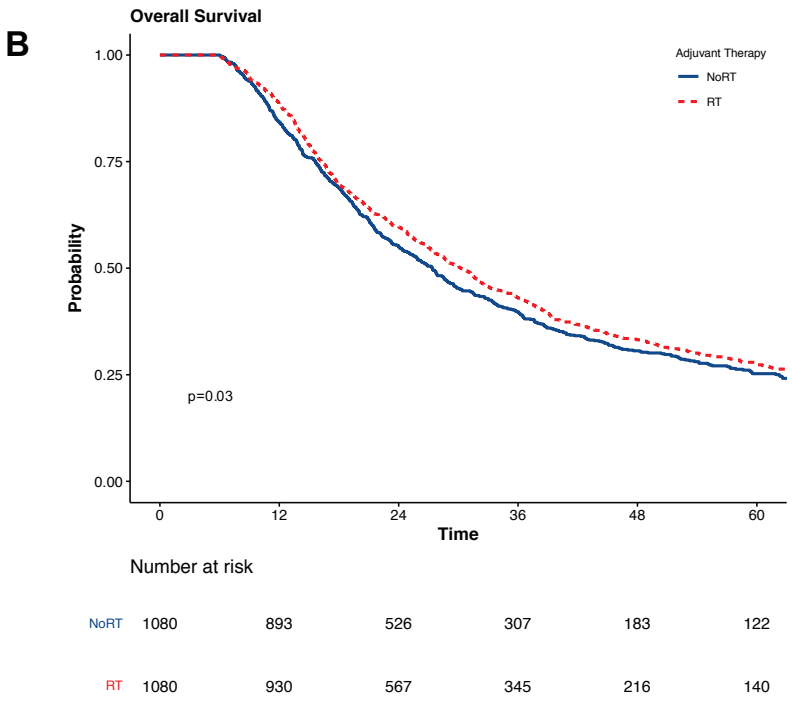

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