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Original Article

Chemoradiotherapy versus chemotherapy alone for unresected intrahepatic cholangiocarcinoma: practice patterns and outcomes from the national cancer data base

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Background: Current guidelines recommend chemotherapy (CT) with or without radiotherapy (RT) for unresected intrahepatic cholangiocarcinoma (IC). Although there is currently lack of consensus, previous smaller studies have illustrated the efficacy of local therapy for this population. This investigation evaluated outcomes of chemoradiotherapy (CRT) versus CT alone in unresected IC using a large, contemporary national database.

Methods: The National Cancer Data Base (NCDB) was queried for primary IC cases (2004–2013) receiving CT alone or CRT. Patients undergoing resection or not receiving CT were excluded, as were those with M1 disease or unknown M classification. Logistic regression analysis ascertained factors associated with CRT administration. Kaplan-Meier analysis evaluated overall survival (OS) between both groups. Cox proportional hazards modeling assessed variables associated with OS.

Results: In total, 2,842 patients were analyzed [n=666 (23%) CRT, n=2,176 (77%) CT]. CRT was less likely delivered at community centers, in more recent time periods (2009–2013), to older patients, and in certain geographic locations. Median OS in the CRT and CT groups were 13.6 *vs.* 10.5 months, respectively (P<0.001). On multivariate analysis, poorer OS was associated with age, male gender, increased comorbidities, treatment at a community center, and treatment at earlier time periods (2004–2008) (P<0.05 for all). Notably, receipt of CRT independently predicted for improved OS (P<0.001).

Conclusions: As compared to CT alone, CRT was independently associated with improved survival in unresected IC. These findings support a randomized trial evaluating this question that is currently accruing.

Keywords: Intrahepatic biliary cancer; intrahepatic cholangiocarcinoma (IC); radiation therapy; chemotherapy (CT); chemoradiotherapy (CRT)

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Introduction

Despite its rarity in the United States, intrahepatic cholangiocarcinoma (IC) is associated with a poor prognosis, especially for unresected disease. The National Comprehensive Cancer Network (NCCN) offers a category 1 recommendation of chemotherapy (CT) alone for this population (1). Chemoradiotherapy (CRT) is a category 2a recommendation, largely owing to no randomized evidence to date.

The addition of local therapy for biliary neoplasms is appealing and an area of active investigation (2,3). Postoperative patterns of recurrence are largely locoregional prior to development of distant metastasis; in fact, initial failure occurs distantly in just 10–15% of cases (4). Locoregional recurrence is also the main cause of tumor-related mortality in these patients (4). Moreover, numerous non-comparative publications have highlighted the safety and efficacy of adding radiotherapy (RT) to CT; these have allowed for high local control, low toxicity rates, and/or numerically prolonged survival (5-12). Many of these studies underscore the importance of providing local therapy to prevent locoregional tumor progression, which can lead to symptomatic worsening and a deterioration in quality of life.

This comparative study of a large, contemporary national database sought to evaluate national practice patterns and outcomes of unresected IC receiving CT alone versus CRT. Although challenging to assess with single- or multi-institutional analyses owing to the relative rarity of this neoplasm, the National Cancer Data Base (NCDB) provides a unique resource with which to address this novel but clinically important issue.

Methods

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the US population (13). All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified dataset, which is then validated. The NCDB contains information not included in the Surveillance, Epidemiology, and End Results (SEER) database, including details regarding use of systemic therapy. The data used in the study were derived from a de-identified NCDB file (2004–2013). The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

Inclusion criteria for this study were patients with newly-diagnosed primary IC. Other biliary neoplasms or hepatocellular carcinoma were not included in the assigned dataset given by the NCDB. Patients that underwent resection (lobectomy, hepatectomy, wedge/segmental resection, or surgery not otherwise specified) were excluded. Patients with M1 disease, unknown M classification, or in situ disease were excluded. Patients without known receipt of CT were eliminated (1,14). Those with missing RT status were also eliminated, as were those coded as palliative in the database. All patients were dichotomized into two groups based on receipt of CT alone versus CRT. In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical, and treatment parameters.

All statistical tests were performed with SAS software (Version 9.4, Cary, NC, USA); tests were two-sided, with a threshold of $P<0.05$ for statistical significance. Univariable and multivariable logistic regression were used to determine characteristics associated with receipt of CRT. All initially examined variables were considered for inclusion into models for stepwise selection (at the 0.05 level), except clinical T and N classification owing to the numerous patients with missing information. Survival analysis (performed with Kaplan-Meier methodology) evaluated overall survival (OS), defined as the interval between the date of diagnosis and the date of death or censored at last contact. Univariate and multivariate Cox proportional hazards modeling evaluated predictors of OS, performed with stepwise selection initially encompassing all available variables.

Results

Figure 1 illustrates the patient selection diagram for this investigation. In total, 2,842 patients met study criteria (*Table 1*); 666 (23%) patients underwent CRT, and 2,176 (77%) received CT alone. Following univariable assessment, multivariable analysis revealed that patients receiving CRT were older, underwent therapy at academic centers, and lived farther from the treating facility ($P<0.05$ for all). There were also regional differences in CRT administration, with decreased use in the Northeast and

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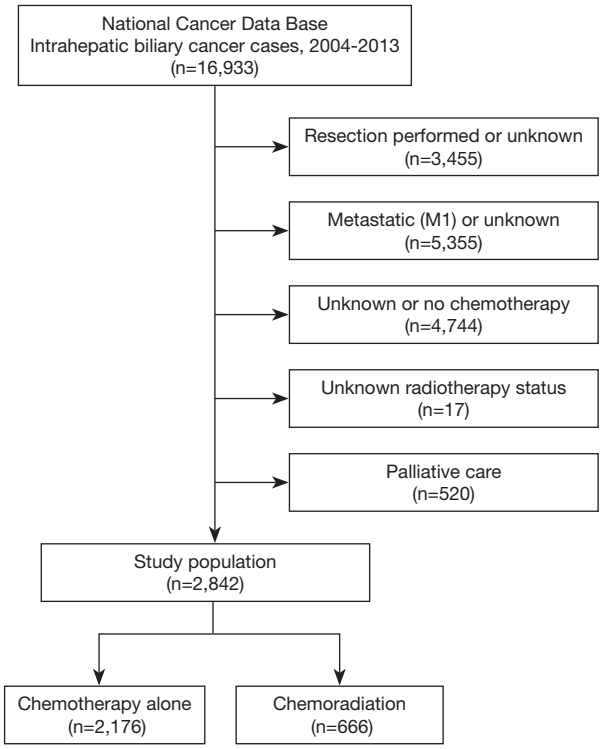

Figure 1 Patient selection diagram.

South as compared to the Midwest; CRT was also delivered less in more recent time periods (2009–2013 *vs.* 2004–2008) (P<0.05 for all).

Kaplan-Meier estimates comparing OS in patients that underwent CT alone versus CRT are displayed in *Figure 2*. The median follow-up was 10 months (range, 0–114 months), the median OS in the respective cohorts was 10.5 [95% confidence interval (CI), 10.0–11.5] months and 13.6 (95% CI, 12.3–15.7) months (P<0.001).

In all patients, there were several predictors of OS on univariate analysis (*Table 2*). Following multivariate analysis (*Table 2*), factors independently associated with decreased OS included advancing age, male gender, increased comorbidities, treatment at a community facility, and diagnosis in earlier years (P<0.05 for all). Of note, receipt of CT alone relative to CRT independently predicted for worse OS (hazard ratio 1.38; 95% CI, 1.24–1.54, P<0.001).

Discussion

Our investigation of a large, contemporary national database of this relatively rare neoplasm is the largest such analysis to date and demonstrates that the addition of RT

Table 1 Characteristics of the overall cohort and factors associated with receiving chemoradiation

Parameter	Chemo alone (N=2,176)	Chemoradiation (N=666)	Univariable		Multivariable (stepwise)	
			OR (95% CI)	P value	OR (95% CI)	P value
Age (years)						
Median [interquartile range]	65 [56–72]	65 [56–73]	1.00 (0.99–1.01)	0.685	1.01 (1.00–1.02)	*0.037*
Gender						
Male	1,081 (50%)	357 (54%)	1.17 (0.98–1.39)	0.076		
Female	1,095 (50%)	309 (46%)	REF	REF		
Race						
White	1,845 (85%)	583 (88%)	1.49 (1.04–2.13)	*0.020*		
Black	184 (8%)	39 (6%)	REF	REF		
Other	125 (6%)	39 (6%)	1.47 (0.89–2.42)	0.365		
Unknown	22 (1%)	5 (1%)	1.07 (0.38–3.00)	0.702		
Charlson Deyo score*						
0	1,566 (72%)	523 (78%)	REF	REF		
1	451 (21%)	105 (16%)	0.71 (0.56–0.89)	*0.020*		
≥2	159 (7%)	38 (6%)	0.72 (0.50–1.04)	0.406		

Table 1 (*continued*)

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Table 1 (*continued*)

Parameter	Chemo alone (N=2,176)	Chemoradiation (N=666)	Univariable		Multivariable (stepwise)	
			OR (95% CI)	P value	OR (95% CI)	P value
Insurance type						
Uninsured	58 (3%)	14 (2%)	REF	REF		
Private	833 (38%)	261 (39%)	1.30 (0.71–2.36)	0.253		
Medicaid/other government	163 (7%)	43 (7%)	1.09 (0.56–2.14)	0.693		
Medicare	977 (45%)	308 (46%)	1.31 (0.72–2.37)	0.216		
Unknown	145 (7%)	40 (6%)	1.14 (0.58–2.26)	0.918		
Income (US dollars/year)						
<$30,000	319 (15%)	93 (14%)	REF	REF		
$30,000–$34,999	491 (23%)	144 (22%)	1.01 (0.75–1.35)	0.190		
$35,000–$45,999	560 (26%)	185 (28%)	1.13 (0.85–1.51)	0.922		
≥$46,000	762 (35%)	222 (33%)	1.00 (0.76–1.32)	0.123		
Unknown	44 (2%)	22 (3%)	1.72 (0.98–3.01)	0.056		
Location						
Metro	1,785 (82%)	544 (82%)	REF	REF		
Urban	277 (13%)	73 (11%)	0.86 (0.66–1.14)	0.119		
Rural	28 (1%)	9 (1%)	1.05 (0.49–2.25)	0.920		
Unknown	86 (4%)	40 (6%)	1.53 (1.04–2.25)	0.053		
Percentage of adults in zip code without high school diploma						
≥21%	389 (18%)	99 (15%)	REF	REF		
13–20.9%	507 (23%)	151 (23%)	1.17 (0.88–1.56)	0.286		
7–12.9%	672 (31%)	218 (33%)	1.27 (0.97–1.67)	0.843		
<7%	565 (26%)	176 (26%)	1.22 (0.93–1.62)	0.531		
Unknown	43 (2%)	22 (3%)	2.01 (1.15–3.52)	*0.039*		
Facility type						
Academic	1,248 (57%)	420 (63%)	REF	REF	REF	REF
Community	863 (40%)	223 (34%)	0.77 (0.64–0.92)	*0.047*	0.78 (0.63–0.96)	*0.021*
Unknown	65 (3%)	23 (4%)	1.05 (0.65–1.71)	0.461	–	–
Facility location						
Northeast	500 (23%)	102 (15%)	0.50 (0.38–0.65)	*<0.001*	0.46 (0.34–0.63)	*<0.001*
South	764 (35%)	225 (34%)	0.72 (0.58–0.90)	*0.036*	0.77 (0.60–0.99)	*0.047*
Midwest	495 (23%)	202 (30%)	REF	REF	REF	REF
West	353 (16%)	114 (17%)	0.79 (0.61–1.03)	0.685	0.84 (0.62–1.14)	0.205
Unknown	64 (3%)	23 (4%)	0.88 (0.53–1.46)	0.452	–	–
Distance to treating facility (miles)						
Median [interquartile range]	13 [5–37]	15 [6–52]	1.00 (1.00–1.00)	*<0.001*	1.00 (1.00–1.00)	*0.002*
Year of diagnosis						
2004–2008	745 (34%)	290 (44%)	REF	REF	REF	REF
2009–2013	1,431 (66%)	376 (57%)	0.67 (0.57–0.81)	*<0.001*	0.58 (0.47–0.71)	*<0.001*

Statistically significant P values (P<0.05) are in italic. Only values included in the final multivariable model are shown. *, The Charlson-Deyo index is a weighted score of comorbidities as defined by several medical codes. OR, odds ratio; CI, confidence interval; REF, reference.

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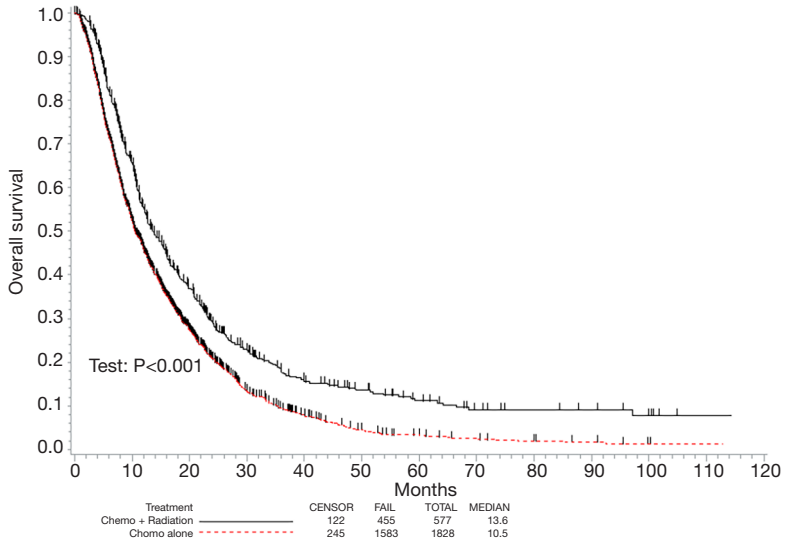

Figure 2 Kaplan-Meier overall survival curve comparing those receiving chemotherapy alone versus chemoradiotherapy.

to CT is independently associated with higher survival in unresected IC. These data directly support the currently accruing phase III trial of stage III-IV unresectable IC receiving gemcitabine/cisplatin with or without tumor-directed RT, whose primary endpoint is OS (15).

While randomized data are needed for this malignancy, it is clear that the retrospective data reported herein may carry selection biases similar to several aforementioned studies, including potentially performing more aggressive therapy in patients that are better able to tolerate multimodality therapy or with better risk features. However, it is also possible that those receiving CRT were a "higher-risk" population with poorer prognostic tumor features and yet still experienced a significantly higher OS (16,17). While we are not able to compare tumor size between cohorts owing to the lack of surgical resection, it is possible that local therapy may have been more often delivered to bulky disease at higher risk for future symptomatology, or from doubt that CT alone could sufficiently control disease progression. To this extent, a limitation of this study is the NCDB's lack of information on tumor size, and that the T and N classifications were also missing in most patients, likely because this cohort consisted of non-operative patients. Additionally, because all patients received CT, it is unlikely that one group was more "unhealthy" than the other, since both cohorts were "fit" enough to receive CT.

Another element that further adds credence to these findings is the study design. Although the NCDB records RT dose information, we intentionally opted not to utilize it as an inclusion/exclusion criterion. Placing a dose threshold may have artificially inflated survival for the CRT cohort, since only the "healthiest" patients would tolerate full-dose RT. Despite evaluating all RT patients, including those with suboptimal dose and/or tolerance, the CRT cohort still experienced statistically higher OS. Other reasons for not evaluating RT dose included existing studies utilizing a wide variety of doses (5-12), the NCCN's lack of a single-best recommended dose for unresected tumors (1), incomplete NCDB dose reporting in many cases, and the overall uncommonness of this malignancy such that further limiting patient numbers would not have allowed adequate sample sizes for comparative analysis.

An interesting area of ongoing investigation of RT for unresected IC is the impact of RT modality. Although conventionally-fractionated RT has been historically utilized, advances in radiation oncology have involved the application of stereotactic body RT (SBRT) (5,8,9,12) and proton beam therapy (PBT) (10,18,19). Both allow for high conformality; SBRT offers the ability to deliver ablative doses in far fewer treatments than conventional fractionation. This is highly important for the practical utility of a local therapy modality; secondary analyses of prospective data have supported high doses per fraction with improved local control and OS (11). Additionally, PBT is being actively investigated for numerous gastrointestinal neoplasms and may allow the maintenance of favorable dosimetric profiles despite large irradiated volumes (20). However, because the NCDB largely has unknown/missing codes for RT modality, this

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Table 2 Univariate and multivariate Cox proportional hazards model for overall survival

Parameter	Univariate		Multivariate (stepwise)	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
Continuous variable	1.01 (1.01–1.02)	*<0.001*	1.01 (1.01–1.02)	*<0.001*
Gender				
Male	1.11 (1.02–1.21)	*0.017*	1.13 (1.03–1.24)	*0.006*
Female	REF	REF	REF	REF
Race				
White	1.13 (0.95–1.33)	0.164		
Black	REF	REF		
Other	0.97 (0.75–1.24)	0.795		
Unknown	0.98 (0.60–1.57)	0.918		
Charlson Deyo score*				
0	REF	REF	REF	REF
1	1.19 (1.06–1.32)	*0.002*	1.13 (1.01-1.27)	*0.030*
≥2	1.39 (1.17–1.65)	*<0.001*	1.31 (1.10-1.56)	*0.003*
Insurance type				
Uninsured	REF	REF		
Private	0.77 (0.58–1.03)	0.079		
Medicaid/other government	0.79 (0.57–1.10)	0.162		
Medicare	0.93 (0.70–1.24)	0.628		
Unknown	0.70 (0.50–0.98)	*0.038*		
Income (US dollars/year)				
<$30,000	REF	REF		
$30,000–$34,999	0.91 (0.79–1.06)	0.219		
$35,000–$45,999	0.86 (0.75–0.99)	*0.039*		
≥$46,000	0.87 (0.76–1.00)	*0.045*		
Unknown	1.07 (0.81–1.41)	0.625		
Location				
Metro	REF	REF		
Urban	1.12 (0.99–1.28)	0.082		
Rural	1.31 (0.90–1.90)	0.160		
Unknown	1.03 (0.84–1.26)	0.797		
Percentage of adults in zip code without high school diploma				
≥21%	REF	REF		
13–20.9%	1.04 (0.90–1.19)	0.614		
7–12.9%	0.99 (0.87–1.13)	0.857		
<7%	0.95 (0.83–1.09)	0.505		
Unknown	1.19 (0.90–1.57)	0.216		
Facility type				
Academic	REF	REF	REF	REF
Community	1.25 (1.14–1.36)	*<0.001*	1.17 (1.07–1.27)	*0.001*

Table 2 (*continued*)

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Table 2 (*continued*)

Parameter	Univariate		Multivariate (stepwise)	
	HR (95% CI)	P value	HR (95% CI)	P value
Unknown	0.98 (0.75–1.26)	0.853	–	–
Facility location				
Northeast	1.04 (0.92–1.19)	0.522		
South	1.03 (0.92–1.16)	0.615		
Midwest	REF	REF		
West	1.08 (0.94–1.24)	0.287		
Unknown	0.94 (0.72–1.22)	0.629		
Distance to treating facility				
Continuous variable	1.00 (1.00–1.00)	*<0.001*		
Year of Diagnosis				
2004–2008	REF	REF	REF	REF
2009–2013	0.91 (0.83–0.98)	*0.034*	0.88 (0.80–0.96)	*0.004*
Treatment group				
Chemotherapy alone	1.41 (1.27–1.57)	*<0.001*	1.38 (1.24–1.54)	*<0.001*
Chemoradiation	REF	REF	REF	REF

Statistically significant P values are in italic. HR, hazard ratio; CI, confidence interval; REF, reference.

work cannot address this issue further.

Lastly, a recent report from Korea demonstrated that delivering combined-modality therapy can allow for tumor downsizing in a small proportion of patients, which can then facilitate the ability to undergo surgical resection (20). Because patients receiving surgery were excluded from this work, we also cannot speak to this notion, but it is certainly conceivable that well-selected patients may benefit from RT so as to allow for resection, making the potential magnitude of benefit for RT even greater than what is reported in this analysis. However, predicting tumor response is more challenging, and hence patient selection for combined-modality treatment must be more completely addressed in future work.

As observed herein, the independent association between treatment at an academic center and OS has far-reaching implications on patient counseling and management by both oncologists and referring providers. Potential causes of this finding are not limited to greater multimodality coordination, streamlined and thorough diagnostic processes, technical expertise, ancillary support staff for close clinical monitoring, and the availability of salvage therapies or clinical trials. Nevertheless, this finding may impact any case of unresected IC and could warrant revisions in patterns of patient education.

Although the NCDB provides a unique platform with which to study this important clinical question, this investigation is not without shortcomings, as described elsewhere (21-43). First, NCDB studies are inherently retrospective, with selection biases and lack of several endpoints such as locoregional control or cancer-specific survival. Second, although we excluded palliative care patients (based on the NCDB variable), definitions of this variable are subject to interpretation and bias. Third, as mentioned extensively above, the NCDB does not keep track of several other factors, including CT details, performance/functional status, RT field design/techniques/volumes. Furthermore, information on T/N-classification and tumor size is largely missing and was hence not able to be analyzed. Additionally, the NCDB does not allow for an assessment of subsequent lines of treatment (e.g., re-irradiation, further systemic and/or targeted therapy), which could also influence OS.

Conclusions

This is the largest study to date evaluating CRT versus CT alone for unresectable IC. Administration of CRT independently predicted for improved survival. However, causation is not implied, and an ongoing phase III study will

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provide definitive evidence regarding this issue.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

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