Chemoradiotherapy Versus Chemotherapy Alone for Unresected Nonmetastatic Gallbladder Cancer: National Practice Patterns and Outcomes

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Abstract

Purpose: Current guidelines recommend chemotherapy (CT) with or without radiotherapy for unresected nonmetastatic gallbladder cancer (GC), with little consensus. However, several small-volume, single-institution studies have documented the efficacy of local therapy for this population. This is the largest study to date evaluating outcomes of chemoradiotherapy (CRT) versus CT alone in unresected nonmetastatic GC. **Methods:** The National Cancer Database was queried for primary GC cases (2004–2013) receiving CT alone or CRT. Patients receiving resection or lack of CT were excluded, as were those with metastatic disease or unknown M classification. Logistic regression analysis ascertained factors associated with CRT delivery. Kaplan-Meier analysis evaluated overall survival (OS) between both cohorts. Cox proportional hazards modeling determined variables associated with OS. **Results:** In total, 1,199 patients were analyzed (CRT: n=327, 27%; CT: n=872, 73%). Groups were evenly balanced, with no factor on multivariate logistic regression analysis statistically predicting for receipt of a particular paradigm. Median OS in the CRT and CT groups was 12.9 versus 7.8 months, respectively ($P=.001$). On multivariate analysis, OS was associated with age and years of treatment ($P=.001$ each). Notably, receipt of CRT independently predicted for improved OS ($P=.001$). **Conclusions:** CRT, compared with CT alone, was independently associated with improved survival in unresected nonmetastatic GC. Although causation is not implied, these results support the necessity for prospective CRT evaluation.

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Although rare in the United States, gallbladder cancer (GC) is associated with relatively poor prognosis, especially for unresected cases. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) treatment recommendations for patients with GC include chemotherapy (CT) alone or chemoradiotherapy (CRT), although it is noted that there are limited data to support the CRT option.¹

Although the addition of local therapy for unresected GC is controversial, it is theoretically appealing for multiple reasons. First, neoplasms of the gallbladder and bile ducts display postoperative patterns of recurrence

that are largely locoregional prior to distant metastasis. It is estimated that just 10% to 15% of cases develop distant metastasis prior to locoregional recurrence, indicating that primary postoperative failure is locoregional.² Additionally, locoregional recurrence is the main cause of tumor-related mortality.² Furthermore, in the operative setting, adjuvant radiotherapy (RT) has been associated with survival benefits, potentially implying some level of cellular response and lack of relative radioresistance.^{3,4}

Although extrapolating these rationales to unresected cases is problematic, foregoing local therapy

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for unresected disease may risk locoregional tumor progression to the point of symptomatic deterioration, quality-of-life decline, and potentially even a survival detriment. There have been numerous retrospective single-institution reports illustrating numerically high survival rates in patients treated with RT.^{5–12} However, these reports have generally been of limited patient numbers and have consisted of carefully selected patient cohorts and/or encompassed multiple types of biliary malignancies.

This comparative study of a large, contemporary national database of a general US population aimed to evaluate national practice patterns and outcomes of unresected nonmetastatic GC receiving CT alone versus CRT. Although challenging to assess with single- or multi-institutional analyses owing to the relative rarity of this malignancy, the National Cancer Database (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 deidentified information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the US population.^{13–31} All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified data set, which is then validated. The NCDB contains information not captured in the SEER database, including details regarding use of systemic therapy. The data used in the study were derived from a deidentified 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 used nor the conclusions drawn from these data by the investigators. Because all patient information in the NCDB is deidentified, this study was exempt from Institutional Review Board evaluation.

Inclusion criteria for this study were patients with newly diagnosed primary GC. Other biliary neoplasms were not included in the assigned data set provided by the NCDB. Patients who underwent resection (defined as wedge/segmental resection, lobectomy, hepatectomy, or surgery not otherwise specified) were excluded, as were those with in situ

Figure 1. Patient selection diagram for this study, describing the application of several exclusion criteria from the initial database cohort to the population analyzed in this study.

disease, M1 disease, or unknown M classification. All patients were required to receive CT, because this is a category 1 recommendation with level I evidence; patients without CT status were removed.^{1,32} Patients were classified into 2 groups based on receipt of additional RT with CT versus lack of RT; patients with a missing RT status were removed. In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical, and treatment data.

All statistical tests were performed with SPSS software (IBM, Armonk, NY); tests were 2-sided, with a threshold of $P < .05$ 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, except clinical T and N classification due to the numerous patients with missing information. Survival analysis (performed using Kaplan-Meier methodology) evaluated overall survival (OS), defined as the interval between date of diagnosis and date of death or censored at last contact.

CRT vs CT Alone for Gallbladder Cancer

Table 1. Patient Characteristics and Factors Associated With Receiving Chemoradiotherapy

Parameter	CRT (N=327)	CT Alone (N=872)	Univariable		Multivariable (Stepwise)	
			OR (95% CI)	P Value	OR (95% CI)	P Value
Median age (range), y	67 (27–90)	66 (26–89)	1.001 (0.989–1.012)	.916		
Sex						
Male	115 (35%)	301 (35%)	0.972 (0.744–1.269)	.833		
Female	212 (65%)	571 (65%)	Ref			
Race						
White	258 (79%)	667 (76%)	0.827 (0.463–1.479)	.522		
Black	48 (15%)	147 (17%)	0.980 (0.511–1.878)	.951		
Other	16 (5%)	50 (6%)	Ref			
Unknown	5 (1%)	8 (1%)	–	–		
Charlson-Deyo score ^a						
0	251 (77%)	673 (77%)	1.087 (0.586–2.015)	.791		
1	61 (19%)	162 (19%)	1.077 (0.552–2.100)	.829		
≥2	15 (5%)	37 (4%)	Ref			
Insurance type						
Uninsured	16 (5%)	40 (5%)	Ref		0.851 (0.438–1.655)	.635
Private	103 (32%)	316 (36%)	1.245 (0.650–2.384)	.509	1.005 (0.534–1.892)	.988
Medicaid/Other government	34 (10%)	67 (8%)	0.987 (0.537–1.812)	.965	0.830 (0.614–1.123)	.228
Medicare	161 (49%)	408 (47%)	1.211 (0.908–1.614)	.193	1.564 (0.967–2.531)	.068
Unknown	13 (4%)	41 (5%)	0.778 (0.495–1.221)	.275	Ref	
Income (\$USD/y)						
<\$30,000	64 (20%)	171 (20%)	0.920 (0.635–1.334)	.661		
\$30,000–\$34,999	62 (19%)	178 (20%)	0.989 (0.681–1.436)	.953		
\$35,000–\$45,999	100 (31%)	234 (27%)	0.806 (0.578–1.124)	.203		
≥\$46,000	93 (28%)	270 (31%)	Ref			
Unknown	8 (2%)	19 (2%)	–	–		
Location						
Metropolitan	260 (80%)	749 (86%)	3.457 (1.046–11.422)	.042	0.299 (0.089–1.004)	.051
Urban	41 (13%)	85 (10%)	2.488 (0.717–8.631)	.151	0.390 (0.111–1.377)	.144
Rural	6 (2%)	5 (1%)	Ref		Ref	
Unknown	20 (6%)	33 (4%)	–	–		
Adults in zip code without high school diploma						
≥21%	73 (22%)	187 (21%)	0.867 (0.586–1.284)	.477		
13%–20.9%	81 (25%)	228 (26%)	0.953 (0.652–1.394)	.805		
7%–12.9%	101 (31%)	249 (29%)	0.853 (0.579–1.204)	.333		
<7%	64 (20%)	189 (22%)	Ref			
Unknown	8 (2%)	19 (2%)	–	–		
Facility type						
Community	133 (41%)	386 (44%)	1.173 (0.905–1.521)	.227		
Academic	190 (58%)	470 (54%)	Ref			
Unknown	4 (1%)	16 (2%)	–	–		
Facility location						
Northeast	70 (21%)	210 (24%)	0.871 (0.568–1.336)	.527	1.073 (0.686–1.680)	.757
South	113 (35%)	285 (33%)	0.732 (0.492–1.089)	.124	1.406 (0.932–2.121)	.105
Midwest	95 (29%)	206 (24%)	0.630 (0.417–0.950)	.027	1.485 (0.968–2.277)	.070
West	45 (14%)	155 (18%)	Ref		Ref	
Unknown	4 (1%)	16 (2%)	–	–		
Median distance to treating facility (range), mi	11 (0–1,300)	9 (0–1,437)	0.999 (0.998–1.001)	.392		
Clinical T classification						
1	8 (2%)	21 (2%)				
2	16 (5%)	23 (3%)				
3	126 (39%)	328 (38%)				
4	66 (20%)	118 (14%)				
Unknown	111 (34%)	382 (44%)				
Clinical N classification						
0	117 (36%)	250 (29%)				
1	81 (25%)	183 (21%)				
2	16 (5%)	49 (6%)				
Unknown	113 (35%)	390 (45%)				
Year of diagnosis						
2004–2008	172 (53%)	411 (47%)	Ref		1.300 (0.994–1.700)	.056
2009–2013	155 (47%)	461 (53%)	0.803 (0.623–1.036)	.092	Ref	

Statistically significant *P* values are in bold.

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; OR, odds ratio.

^aThe Charlson-Deyo index is a weighted score of comorbidities as defined by several medical codes.

Univariate and multivariate Cox proportional hazards modeling was used to evaluate predictors of OS.

Results

A complete flow diagram of patient selection is provided in Figure 1. In total, 1,199 patients met study analysis criteria; 327 patients (27%) underwent CRT, whereas 872 (73%) received CT alone (Table 1). Following univariate analysis, multivariable assessment revealed that no factors were independently associated with CRT delivery; this implied that the CRT and CT populations were substantially well balanced. There were, however, trends toward increasing receipt of CRT in Medicare patients ($P=.068$) and those living in the Midwest ($P=.070$). Trends were also noted for decreased CRT in the metropolitan population ($P=.051$) and those treated during more recent periods (2009–2013 vs 2004–2008; $P=.056$).

Median follow-up was 9 months for all patients (range, 0–123 months). Kaplan-Meier estimates comparing OS in patients who received CT alone versus CRT are illustrated in Figure 2; median OS in the respective cohorts were 7.8 months (95% CI, 7.1–8.5) and 12.9 months (95% CI, 11.0–14.7; $P=.001$).

Figure 2. Kaplan-Meier overall survival curve comparing those receiving chemotherapy alone (green) versus chemoradiotherapy (blue), demonstrating statistically superior survival in patients receiving chemoradiotherapy.

In the overall cohort, there were several predictors of OS on univariate analysis (Table 2). After multivariate adjustment for potential confounding factors, factors independently associated with poorer OS included advancing age and diagnosis in prior years ($P=.001$ for both). Of note, receipt of CRT relative to CT alone independently predicted for improved OS (hazard ratio [HR], 0.721; 95% CI, 0.532–0.979; $P=.001$).

Discussion

Our study of a large, contemporary national database for this relatively rare malignancy—the largest such analysis to date—most notably demonstrates that the addition of RT to CT is independently associated with higher survival in unresected GC. This finding suggests that these hypothesis-generating data should ideally be tested in a prospective study.

These retrospective data may carry selection biases similar to several aforementioned studies, including the potential to perform more aggressive therapy in patients with better risk features or who are better able to tolerate multimodality therapy. In contrast, it is possible that the CRT population was a “higher-risk” cohort and yet still experienced a significantly higher OS.^{33,34} It is intuitive that local therapy may be more often delivered in bulkier cases at higher risk for future/current symptomatology, or potentially owing to doubt that CT alone could sufficiently control the disease. To this extent, a shortcoming of this investigation is the NCDB’s lack of information regarding tumor size, which may impact the efficacy of additional RT in this setting³⁵; the T and N classifications were also largely missing, likely owing to the nonoperative nature of this cohort. Additionally, overall, patients were well balanced (and therefore there was no statistically valid role for propensity matching), without differences in age or comorbidity index. Because all patients received CT, it cannot be said that one group was more “unhealthy” than the other, as both groups were “fit” enough to receive CT. Furthermore, another salient factor was that CRT was less likely given at later periods (2009–2013; $P=.056$), but treatment during these periods was independently associated with increased OS on multivariate analysis ($P=.001$).

The study design further adds credence to the findings regarding CRT versus CT. Although the

CRT vs CT Alone for Gallbladder Cancer

Table 2. Univariate and Multivariate Cox Proportional Hazards Model for Overall Survival

Parameter	Univariate			Multivariate		
	HR	95% CI	P Value	HR	95% CI	P Value
Treatment group (CRT vs CT alone)	0.557	0.480–0.646	.001	0.721	0.532–0.979	.001
Age (continuous)	1.016	1.010–1.022	.001	1.063	1.037–1.090	.001
Sex (male vs female)	0.957	0.837–1.093	.516			
Race						
Black vs white	0.873	0.662–1.151	.336			
Others vs white	0.855	0.626–1.166	.322			
Charlson-Deyo score						
0 vs 2	1.014	0.743–1.385	.931			
1 vs 2	1.268	0.905–1.776	.167			
Insurance						
Uninsured vs private	0.844	0.620–1.150	.284			
Uninsured vs Medicaid/other government	0.902	0.658–1.238	.524			
Uninsured vs Medicare	0.791	0.686–0.911	.001			
Income, \$USD						
<\$30,000 vs \$30,000–\$34,999	1.047	0.870–1.260	.626			
<\$30,000 vs \$35,000–\$45,999	0.945	0.785–1.138	.552			
<\$30,000 vs ≥\$46,000	0.929	0.785–1.100	.393			
Location						
Urban vs metropolitan	0.679	0.352–1.311	.249	0.522	0.270–1.010	.054
Rural vs metropolitan	0.750	0.380–1.482	.408	0.613	0.310–1.213	.160
Adults in zip code without high school diploma						
13%–20.9% vs ≥21%	1.039	0.852–1.266	.708			
7%–12.9% vs ≥21%	1.019	0.844–1.230	.847			
<7% vs ≥21%	1.061	0.883–1.275	.525			
Facility type (community vs academic)	1.148	1.008–1.306	.037			
Facility location						
South vs Northeast	0.917	0.746–1.127	.410			
Midwest vs Northeast	0.987	0.815–1.196	.895			
West vs Northeast	0.944	0.771–1.155	.573			
Distance to treatment facility (continuous)	1.000	0.999–1.000	.515			
Year of diagnosis (2004–2008 vs 2009–2013)	1.211	1.064–1.379	.004	1.275	1.115–1.458	.001

Statistically significant *P* values are in bold. Only values included in the final multivariate model are shown. Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio.

NCDB records RT dose information, we specifically opted not to use this as an inclusion/exclusion criterion. Placing a cutoff may have artificially inflated survival for the CRT group, because the “healthiest” patients would be able to receive and tolerate full-dose RT. By including all patients who underwent RT, we intentionally included those with suboptimal dose and/or tolerance. Despite this, the CRT cohort still displayed a markedly higher OS. Other reasons for not including a dose-based cutoff were that existing studies often use a wide variety of doses,^{5–12} NCCN does not routinely recommend a particular dose for unresected cases,¹ there was a lack of dose reporting in many cases, and this neoplasm is rare, and therefore limiting patient numbers would not have allowed for adequate sample sizes for comparative analyses. Dose-escalation may be advantageous in these patients to provide “durable local control,” which is unsubstantiated in this circumstance but

needs further evaluation. Lastly, there was a small group of patients who displayed long-term survival in this study (corresponding to the “tail” in the CRT curve in Figure 2), indicating that local therapy could potentially be curative in a subset of patients.

Although this is the only study of its kind, 2 SEER publications previously attempted to address this question specifically for extrahepatic cholangiocarcinoma.^{36,37} Although both studies found OS improvements with RT versus without, a major advantage of our study is that the SEER database does not contain any information on CT. As such, a proportion of patients in the “no RT” groups in those analyses might not have received any tumor-directed therapy (ie, received supportive care alone). There is reason to believe that many patients in that cohort received supportive care, because not only is it still recommended by the NCCN Guidelines¹ but also it may have been the standard of care prior to a ran-

domized trial showing it to be inferior to CT (albeit in a mix of hepatopancreatobiliary neoplasms).³² That trial was published in 1996,³³ whereas both aforementioned SEER studies extracted patients from as early as 1988³⁶ and 1973.³⁷ This bias clearly leads to difficulties in interpretation, and to this extent the information on receipt of CT provided by the NCDB allowed for the selection of a “pure,” more modern cohort of patients who all received CT at baseline. Although the NCDB does not provide information on number of cycles, specific agents, or tolerance to CT, it still offers a marked benefit over existing SEER reports.

Consequently, although the NCDB provides a unique platform on which to study this important clinical question, this investigation is not without limitations. First, NCDB studies are inherently retrospective, with selection biases and lack of several end points, such as locoregional control or cancer-specific survival. Second, although we excluded patients undergoing palliative care (per the NCDB variable), definitions of this variable are subject to interpretation and bias. Third, as mentioned previ-

ously, the NCDB does not keep track of several other factors, including CT details, performance/functionality status, and RT field design/volumes/techniques. Furthermore, information on histology, T/N classification, and tumor size is missing, largely owing to the nonoperative nature of these patients, and was thus not able to be thoroughly analyzed. Additionally, the NCDB does not allow for assessment of subsequent lines of treatment (eg, reirradiation, further systemic and/or targeted therapy), which could influence OS.

Conclusions

This is the largest study to date evaluating the utility of CRT compared with CT alone for treating unresectable nonmetastatic GC. Administration of CRT was independently associated with improved survival. Nevertheless, causation is not implied, and prospective evidence is necessary to verify the conclusions presented herein. The accruing NRG-GI001 randomized trial is evaluating a similar question for intrahepatic cholangiocarcinoma (ClinicalTrials.gov identifier: NCT02200042).

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CRT vs CT Alone for Gallbladder Cancer

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