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Definitive Liver Radiotherapy for Intrahepatic Cholangiocarcinoma with Extrahepatic Metastases

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Abstract

Introduction: Tumor-related liver failure (TRLF) is the most common cause of death in patients with intrahepatic cholangiocarcinoma (ICC). Though we previously showed that liver radiotherapy (L-RT) for locally advanced ICC is associated with less frequent TRLF and longer overall survival (OS), the role of L-RT for patients with extrahepatic metastatic disease (M1) remains undefined. We sought to compare outcomes for M1 ICC patients treated with and without L-RT. ***Methods:*** We reviewed ICC patients that found to have M1 disease at initial diagnosis at a single institution between 2010 and 2021 who received L-RT, matching them with an institutional cohort by propensity score and a National Cancer Database (NCDB) cohort by frequency technique. The median biologically effective dose was 97.5 Gy (interquartile range 80.5–97.9 Gy) for L-RT. Patients treated with other local therapies or supportive care alone were excluded. We analyzed survival with Cox proportional hazard modeling. ***Results:*** We identified 61 patients who received L-RT and 220 who received chemotherapy alone. At

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median follow-up of 11 months after diagnosis, median OS was 9 months (95% confidence interval [CI] 8–11) and 21 months (CI: 17–26) for patients receiving chemotherapy alone and L-RT, respectively. TRLF was the cause of death more often in the patients who received chemotherapy alone compared to those who received L-RT (82% vs. 47%; $p = 0.001$). On multivariable propensity score-matched analysis, associations with lower risk of death included duration of upfront chemotherapy (hazard ratio [HR] 0.82; $p = 0.005$) and receipt of L-RT (HR: 0.40; $p = 0.002$). The median OS from diagnosis for NCDB chemotherapy alone cohort was shorter than that of the institutional L-RT cohort (9 vs. 22 months; $p < 0.001$). ***Conclusion:*** For M1 ICC, L-RT associated with a lower rate of death due to TRLF and longer OS versus those treated with chemotherapy alone. Prospective studies of L-RT in this setting are warranted.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy, for which incidence and mortality have increased over the last 4 decades [1–3]. For patients with unresectable disease, several studies have shown that control of the primary tumor extends survival [4–7]. For the 20–30% of patients with ICC who present with metastatic extrahepatic disease (M1), however, limited evidence for benefit with local therapy exists [8]. The median overall survival (OS) time for patients with M1 ICC is estimated to be 3–9 months and 5-year OS is estimated to be 3% [8–11]. The standard of care for the treatment of these patients is palliative chemotherapy alone [12].

Approximately 80% of patients with M1 ICC treated with chemotherapy alone die of tumor-related liver failure (TRLF) related to inadequate control of primary or satellite lesions, which obstruct or destroy neighboring parenchyma, vasculature, or bile ducts [7]. Recent studies have suggested a potential oncologic benefit with the use of liver radiotherapy (L-RT) for patients with unresectable ICC, which is hypothesized to improve survival outcomes by mitigating death due to TRLF [4–6, 13]. However, few studies have studied the efficacy of liver-directed therapies for M1 ICC [8] and the role of L-RT specifically remains poorly defined. Thus, we reviewed our institutional experience of patients with M1 ICC to determine differences in rates of TRLF and survival among patients treated with and without L-RT.

Methods

Patient Selection

After approval by the Institutional Review Board (PA14-0646), we identified 281 consecutive patients aged ≥18 years with biopsy-confirmed M1 ICC at initial presentation treated with either chemotherapy alone or chemotherapy followed by L-RT between 2010 and 2021 at MD Anderson Cancer Center. M1 disease was defined as any distant organ or non-regional lymph node metastasis. Based on the American Joint Committee on Cancer (AJCC) 8th edition staging system, lymph node metastases distant to the hepatoduodenal ligament were considered to be staged as M1. Common hepatic, celiac, and para-aortic lymph nodes were considered distant for all tumors, whereas cardiac, cardio-phrenic, diaphragmatic, and lesser curvature lymph nodes were considered distant only for right-sided tumors. Patients with isolated involved hepatoduodenal and portal venous lymph nodes were considered to be staged as N1 and excluded. Patients with intrahepatic metastases without distant extrahepatic disease were excluded.

All patients were evaluated in a multidisciplinary manner primarily by surgical and medical oncologists. Evaluation consisted of complete history and physical examination, laboratory studies including liver function tests and tumor markers, mutational profiling using next-generation sequencing, pathology review by dedicated hepatobiliary pathologists, computed tomography (CT) imaging of the chest/abdomen/pelvis with contrast ± liver magnetic resonance imaging. Patients deemed to have M1 ICC with unresectable liver disease were typically initiated on chemotherapy and evaluated using serial CT imaging every 3 months or sooner in cases of suspected disease progression. Selection of chemotherapy was at the discretion of the treating medical oncologist, reflecting patient tolerability and comorbidities. Subsequently, patients were discussed at a multidisciplinary tumor board and referred to radiation oncology for consideration of consolidative L-RT to the dominant liver mass upon group consensus.

L-RT Details

Prior to initiation of L-RT, radiographic response to upfront chemotherapy was assessed by a board-certified hepatobiliary radiologist using RECIST 1.1 criteria [14]. The selection of patients for L-RT in this study reflects our clinical practice to identify patients who have had stable or better disease after chemotherapy, with the idea to consolidate lesions that may threaten liver vasculature, bile ducts, or functional parenchyma while meeting constraints for uninvolved liver. All of the patients in this study received courses of radiotherapy that utilized higher doses (median BED_{10} 97.5 Gy) than typical palliative regimens such as 20 Gy in 5 fractions (BED_{10} 28 Gy) or 30 Gy in 10 fractions (BED_{10} 39 Gy). L-RT simulation and treatment details have been previously described [5, 15]. All patients were treated using either intensity-modulated radiation therapy or passive scatter proton beam therapy, based on physician preference. Biologically effective dose (BED_{10}) was calculated using an α/β ratio of 10 for tumor, and patients receiving a BED_{10} of <50 Gy were excluded. Patients receiving L-RT did so at a median 9 months after initial diagnosis to a median BED_{10} of 97.5 Gy (interquartile range 80.5–97.9 Gy); 74% of patients received a BED_{10} of ≥80.5 Gy. All post-RT scans were reviewed by a hepatobiliary radiologist and by the treating radiation oncologist.

Disease-Related Outcomes

Among all patients in this study, the primary endpoints were OS and cause of disease-related death. TRLF was considered the cause of death in the presence of findings including portal hypertension (variceal bleed, splenomegaly, or low platelet count), refractory ascites, hepatic encephalopathy, or obstructive liver disease [16]. Death was attributed to progression at sites (extrahepatic bile duct, peritoneum, lung, other extrahepatic site) based upon evidence of disease progression on imaging within 3 months of death in conjunction with compatible clinical symptoms. In cases of ambiguity (i.e., death was equally likely due from progression at more than one site), multiple likely causes were recorded. Deaths due to non-cancer causes were also recorded. For expired patients without disease-related follow-up within 3 months of death, the cause was recorded as unknown. OS was defined as the time from initial diagnosis to death of any cause or last follow-up.

Local control (LC), intrahepatic distant progression-free survival (DPFS), and extrahepatic DPFS were additionally calculated. LC was defined as the time between the initiation of chemotherapy and radiographic detection of local progression at the dominant liver lesion or last follow-up. Intrahepatic DPFS was defined as the time between chemotherapy initiation and radiographic detection of liver progression outside the dominant lesion or death. Extrahepatic DPFS was defined as the time between chemotherapy initiation and radiographic detection of progression at a distant site or death.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics. Fisher exact tests were used to assess the associations between categorical variables, and Wilcoxon rank-sum tests were utilized to assess associations between continuous variables between the two treatment cohorts. Univariate and multivariable logistic regressions were used to identify factors associated with receipt of L-RT. Time-to-event endpoints were analyzed using the Kaplan-Meier method. Univariate and multivariable Cox proportional hazard analyses were used to determine associations with outcomes. The proportional hazard assumptions for all univariate and multivariable models were evaluated using χ^2 tests of Schoenfeld residuals. Tests of the proportional hazard assumptions for death, local progression, intrahepatic DPFS, and extrahepatic DPFS using Schoenfeld residuals all yielded $p > 0.05$, and thus, we failed to reject the null hypotheses that the hazards were proportional. We used a p value threshold of ≤0.05 on univariate analysis to select variables for inclusion in each corresponding multivariable model. A landmark analysis for OS at 6 months following diagnosis was performed. Statistical analysis was performed with Stata Version 17.0 (StataCorp, College Station, TX, USA) and SAS 9.4 (Sas Institute, Cary, NC, USA).

As a sensitivity analysis, we performed propensity score matching using age at diagnosis, sex, tumor size, baseline CA: 19–9, T-stage, vascular tumor thrombus, and satellitosis to predict the probability of receiving radiation therapy. The greedy nearest neighbor matching method with caliper width 0.25 without replacement was utilized to match cases and controls at a 1:2 ratio between patients receiving L-RT and receiving chemotherapy alone [17]. For the institutional chemotherapy alone versus L-RT propensity-matched comparison, sex (male or female), T-stage (1, 2, 3, or 4), vascular tumor thrombus (yes or no), and satellitosis (yes or no) were entered as categorical variables, whereas age, size, and CA: 19–9 were entered as continuous variables. Due to missing values, one observation was excluded from the L-RT cohort and 15 observations were excluded from the chemotherapy alone cohort. After applying the match, cases in the support region of each cohort were identified and cases with extreme predicted probability values were excluded. This was conducted using 1:1, 1:2, and 1:3 ratio matching, which yielded samples of 114 patients (57 in each cohort), 168 patients (56 L-RT and 112 chemotherapy alone), and 108 patients (27 L-RT and 81 chemotherapy alone), respectively. Accordingly, we chose to proceed with the 1:2 match to maintain as large a sample size as possible. Analyses of OS using PS-matched Kaplan-Meier and Cox proportional hazard regression analyses were also performed using a 6-month conditional landmark.

National Cancer Database Comparison

A frequency-matched comparison using registry data from the National Cancer Database (NCDB) was performed by matching on age, sex, year of diagnosis, tumor diameter, and T-stage. For the frequency-matched NCDB comparison, the 2004–2019 intrahepatic bile duct participant user file of the NCDB was queried for patients diagnosed with M1 ICC between 2010 and 2018; survival follow-up data were unavailable for patients diagnosed in 2019; patients who received multiagent chemotherapy, did not undergo any liver-directed therapy (including RT, surgery, or trans-arterial therapy), and had follow-up data were included. We excluded patients with incomplete staging information (i.e., for T-, N-, or M-stage). Frequency matching was used to generate an NCDB cohort of M1 ICC patients treated with chemotherapy after matching by age (<50, ≥50 and <60, ≥60, and <70, ≥70), sex (male or female), year of diagnosis (≤2015 or ≥2016), tumor diameter (≤5 cm, between 5 and 10 cm, or ≥10 cm), and T-stage (1, 2, 3, or 4). NCDB cohort selection is shown in online supplementary Figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000530134). We selected a 1:3 matching ratio, which yielded 57 institutional patients receiving L-RT and 171 NCDB patients receiving chemotherapy alone. While we initially sought to include L-RT patients in the frequency-matched analysis, substantial size and T-stage data were missing for these patients, resulting in a sample of just 23 patients available for matching. Given concerns about selection bias, we elected to omit NCDB L-RT patients from this analysis. Analyses of OS using frequency-matched cohorts were performed using a 6-month conditional landmark. Kaplan-Meier curves were constructed, and stratified log-rank tests were performed to compare survival.

Molecular Analysis

Molecular testing results were available for the majority of patients in this study. Methods are detailed in the online supplement.

Results

Patient and Treatment Characteristics

Baseline patient characteristics are shown in Table 1. Of 281 total patients identified, 220 (78%) received chemotherapy alone and 61 (22%) received chemotherapy followed

Table 1. Baseline characteristics and treatment details for institutional cohort of M1 ICC patients, stratified by treatment group. Categorical variables were compared using Fisher's exact tests, and continuous variables were compared using the Wilcoxon rank-sum test

Attribute	Chemotherapy only (n = 220)	Chemotherapy + L-RT (n = 61)	p value
Median age at diagnosis (IQR), years	61 (52–67)	63 (56–70)	0.107
Sex, *n* (%)			
Male	121 (55)	32 (52)	0.772
Female	99 (45)	48 (48)	
ECOG performance status, *n* (%)			
0–1	185 (84)	54 (89)	0.542
2–3	35 (16)	7 (11)	
Median baseline CA 19–9 (IQR), U/mL	168 (52–1,583)	66 (19–837)	0.031*
Median tumor size in greatest dimension (IQR), cm	8.4 (5.6–11.9)	8.3 (6.1–12)	0.952
T-stage, *n* (%)			
1–2	171 (78)	46 (75)	0.731
3–4	49 (22)	15 (25)	
N stage, *n* (%)			
0	32 (15)	10 (16)	0.689
1	188 (85)	51 (84)	
Sites of metastasis at diagnosis, *n* (%)			
Non-regional nodes	137 (62)	29 (48)	0.038*
Peritoneal	83 (38)	14 (23)	0.032*
Lung	96 (44)	29 (48)	0.587
Bone	77 (35)	7 (11)	<0.001*
Portal vein thrombus at diagnosis	24 (11)	13 (21)	0.052
Satellite lesions at diagnosis	143 (65)	41 (67)	0.879
Child-Pugh score prior to treatment initiation (n = 192 for chemotherapy alone, n = 51 for L-RT), *n* (%)			
5A	90 (47)	25 (49)	0.972
6A	52 (27)	16 (31)	
7B	24 (13)	6 (12)	
8B	18 (9)	3 (6)	
9B	5 (3)	1 (2)	
10C	3 (2)	0 (0)	
Mutations present (n = 151 for chemotherapy alone, n = 50 for L-RT), *n* (%)			
TP53	47 (31)	15 (30)	0.881
IDH1	28 (19)	15 (30)	0.087
CDKN2A	38 (25)	5 (10)	0.023*
KRAS	33 (22)	8 (16)	0.373
ARID1A	24 (16)	10 (20)	0.502
BAP1	24 (16)	5 (10)	0.304
FGFR2	26 (17)	4 (8)	0.113
Type of 1st line chemotherapy used, *n* (%)			
Gemcitabine/cisplatin±nab-paclitaxel	171 (78)	55 (90)	0.030*
Other	49 (22)	6 (10)	
Median duration of 1st line chemotherapy (IQR), months	2.7 (1.6–5.8)	4.6 (2.5–7.4)	<0.001*
Radiotherapy details			
Time from diagnosis to RT, months		8.7 (6.2–11.3)	
Median dose, Gy (IQR)		62.5 (50.4–67.5)	
Median number of fractions (IQR)		15 (15–15)	
Median BED_{10}, Gy (IQR)		97.5 (78.1–97.9)	
Received ablative RT (≥80.5 Gy BED_{10})		45 (74%)	

by L-RT. Characteristics between treatment cohorts were generally well balanced. Importantly, no significant difference in pre-treatment liver function, as measured by Child-Pugh score, was seen between the cohorts (p = 0.972). Notable differences between the chemotherapy alone arm versus the L-RT arm included higher median baseline CA:

19–9 (168 vs. 66 U/mL; $p = 0.031$), higher proportions of non-regional nodal (62% vs. 48%; $p = 0.038$), peritoneal (38% vs. 23%; $p = 0.032$), and osseous (35% vs. 11%; $p = 0.038$) metastases, less frequent 1st line administration of gemcitabine/cisplatin (78% vs. 90%; $p = 0.030$), and longer duration of 1st line chemotherapy (2.7 vs. 4.6 months; $p < 0.001$). For patients who went on to receive L-RT, response to chemotherapy was partial response in 4 (7%) patients, stable disease in 44 (72%) patients, and progressive disease in 13 (21%) patients per RECIST 1.1 criteria. A multivariable logistic regression (online suppl. Table 1) revealed that patients with non-regional nodal, peritoneal, and osseous metastases were less likely to receive L-RT.

Disease Control and Survival

At median follow-up of 11 months after diagnosis, median OS was 9 months (95% confidence interval [CI] 8–11) and 21 months (CI: 17–26) for patients receiving chemotherapy alone and L-RT, respectively. OS after diagnosis at 1 and 2 years was 39% (CI: 32–45%) and 15% (CI: 11–20%) following chemotherapy alone and 85% (CI: 74–92%) and 42% (CI: 29–54%) following L-RT, respectively (Fig. 1). Median LC was 8 months (CI: 6–9) and 36 months (CI: 19–undefined) for patients receiving chemotherapy alone and L-RT, respectively. LC at 1 and 2 years was 34% (CI: 27–41%) and 11% (CI: 6–17%), respectively, following chemotherapy alone, and 81% (CI: 68–89%) and 53% (CI: 37–68%), respectively, following L-RT. Results for intrahepatic progression-free survival and extrahepatic progression-free survival similarly favored the L-RT cohort (Table 2; online suppl. Fig. 2).

Patterns of first progression following initiation of chemotherapy were similar between cohorts (online suppl. Table 2); of patients who experienced progression did so at liver, distant, and concurrently at liver and distant sites with roughly equal frequency. A comparison of OS for patients experiencing these three grouped patterns of progression did not reveal significant differences (online suppl. Fig. 3). Patients who did not have radiographically confirmed progression at last follow-up had apparently shorter survival; however, the probable reason for this finding was that the vast majority of these died shortly after initial presentation.

Among patients receiving L-RT, radiographic response to chemotherapy (i.e., partial response, stable disease, or progressive disease) did not correlate with OS ($p = 0.147$) after initial diagnosis nor did it correlate with LC ($p = 0.578$), intrahepatic DPFS ($p = 0.893$), or extrahepatic DPFS ($p = 0.434$) after L-RT. Multivariable Cox proportional hazard modeling for factors associated with OS following diagnosis is shown in Table 3. Associations with higher risk of death included age (hazard ratio [HR] 1.01; $p = 0.026$) and ECOG 2–3 (HR: 1.82; $p < 0.001$); associations with lower risk included longer chemotherapy duration (HR: 0.41; $p < 0.001$) and L-RT (HR: 0.41; $p < 0.001$). Conditional landmark analysis at 6 months following diagnosis included 69% of the full chemotherapy alone cohort and 98% of the full L-RT cohort. A difference in OS between the chemotherapy alone and L-RT cohorts persisted with conditional landmark analysis at 6 months ($p < 0.001$). On multivariable Cox proportional hazards analysis with a 6-month landmark (online suppl. Table 3), L-RT was associated with a lower risk of death (HR 0.59, CI: 0.40–0.86; $p = 0.007$). Multivariable Cox analysis for LC (online suppl. Table 4), intrahepatic DPFS (online suppl. Table 5), and extrahepatic DPFS (online suppl. Table 6) all revealed that longer chemotherapy duration and use of L-RT were associated with lower risk of progression.

After propensity score matching, analytic cohorts of 112 patients treated with chemotherapy alone and 56 patients treated with L-RT were selected. Baseline characteristics (online suppl. Table 7) of matched cohorts were well balanced with the exception of a higher proportion of patients with bone metastases (38% vs. 13%; $p < 0.001$) and a lower proportion of patients receiving gemcitabine/cisplatin (75% vs. 91%; $p = 0.014$) among the chemotherapy alone cohort. Notably, the median duration of 1st line chemotherapy was not significantly different between matched cohorts (3.4 vs. 4.1 months; $p = 0.127$). Stratified Cox analyses (online suppl. Table 8) revealed only longer chemotherapy duration (HR: 0.73; $p < 0.001$) and receipt of L-RT (HR: 0.29; $p < 0.001$) to be associated with a lower risk of death. Concordant results were seen with a 6-month landmark analysis (online suppl. Table 9). OS curves (online suppl. Fig. 4) for propensity score-matched cohorts are also provided. Disease-related outcomes after propensity score matching (online suppl. Table 10) are concordant with the primary analysis. Additional sensitivity analyses were performed to further match patients in the presence of bone metastases and receipt of gemcitabine/cisplatin (online suppl. Table 11), with concordant findings on survival analysis (online suppl. Table 12).

We also compared our institutional L-RT cohort to patients with M1 ICC treated with chemotherapy alone from the NCDB. A total of 1,696 cases from the NCDB met inclusion criteria (online suppl. Fig. 1), from which 171 matched patients were selected for analysis. The median OS from diagnosis for the NCDB chemotherapy alone cohort was significantly shorter than that of the institutional L-RT cohort (9 vs. 22 months; $p < 0.001$), a

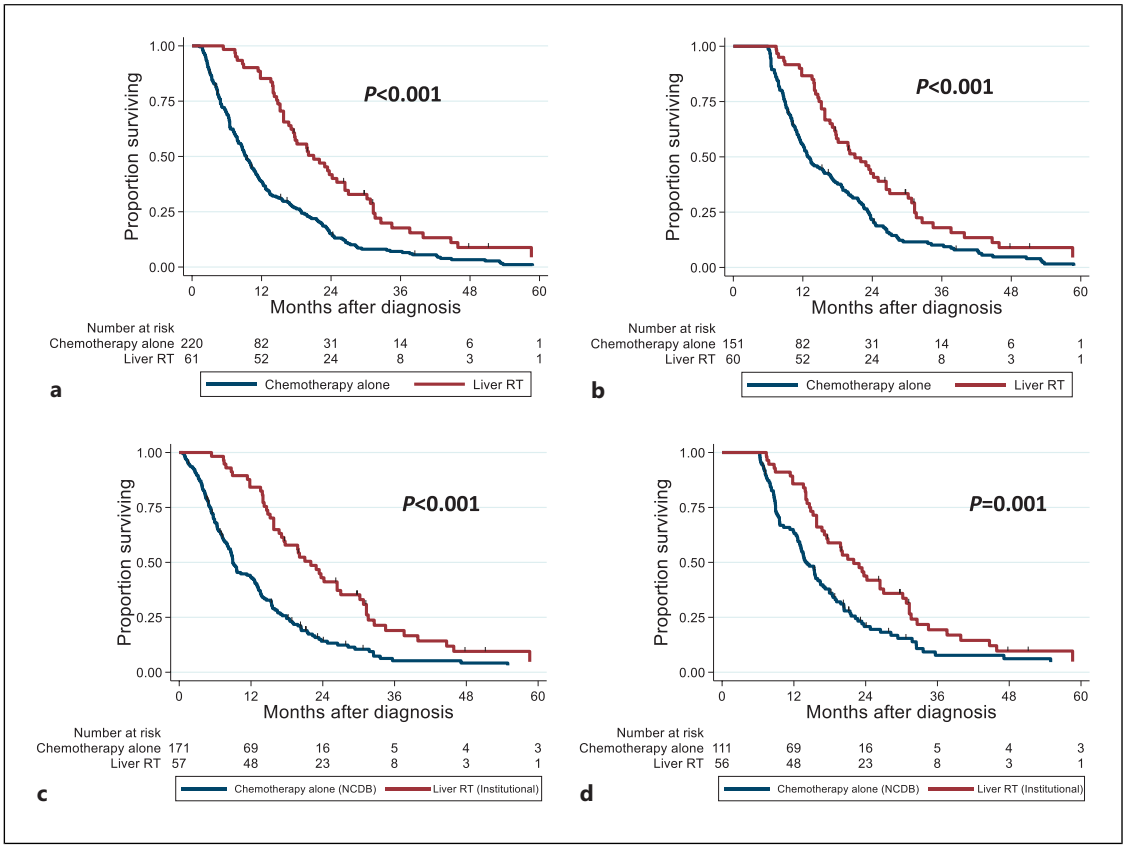


Fig. 1. Kaplan-Meier overall survival curves for institutional patients comparing chemotherapy alone and L-RT without landmark (**a**) and with landmark (**b**) at 6 months. Also shown are frequency-matched cohorts of institutional patients receiving L-RT and National Cancer Database patients receiving chemotherapy alone without landmark (**c**) and with landmark (**d**) at 6 months. All log-rank analyses revealed significantly longer survival for patients treated with L-RT.

difference which persisted on conditional landmark analysis at 6 months (14 vs. 22 months; $p < 0.001$; Fig. 1c, d).

Causes of Death

Causes of death for patients treated with chemotherapy alone versus with L-RT are shown in Figure 2. L-RT was associated with a lower rate of TRLF (82% vs. 47%; $p < 0.001$) but a higher rate of death due to progressive disease in the peritoneum (12% vs. 25%; $p = 0.028$) and lung (17% vs. 30%; $p = 0.033$). No significant difference was seen for rates of deaths due to extrahepatic biliary disease, disease at other extrahepatic sites, or unknown causes between treatment cohorts. Among the 212 patients who died of TRLF, the time to death was significantly shorter for patients receiving chemotherapy alone versus those receiving L-RT (9 vs. 18 months; $p = 0.002$). Among the 40 patients who died of extrahepatic biliary disease, the time to death was significantly shorter for patients receiving chemotherapy alone versus those receiving L-RT (9 vs. 31 months; $p = 0.046$). There were no significant differences between treatment cohorts in time to death among patients who died of peritoneal, lung, other extrahepatic, or unknown causes. Relationships between initial sites of disease, treatment cohort, and cause of death are shown in Figure 3.

Mutational Profiling

Mutational profiling results are shown in online Supplemental Table 13, Figure 5, and Table 14.

Discussion

Several studies have shown that use of L-RT for the treatment of locally advanced ICC is both safe and

Table 2. Summary of disease-related outcomes stratified by treatment cohort

Endpoint (95% CI, unless otherwise noted)	Chemotherapy alone (n = 220)	L-RT (n = 61)
Following diagnosis		
Follow-up time (IQR), months	9 (5–18)	20 (15–30)
Median overall survival, months	9 (8–11)	21 (17–26)
Overall survival at 12 months, %	39 (32–45)	85 (74–92)
Overall survival at 24 months, %	15 (11–20)	42 (29–54)
Following chemotherapy initiation		
Median local control, months	8 (6–9)	36 (19-undefined)*
Local control at 12 months, %	34 (27–41)	81 (68–89)
Local control at 24 months, %	11 (6–17)	53 (37–68)
Median intrahepatic progression-free survival, months	4 (4–6)	13 (11–15)
Intrahepatic progression-free survival at 12 months, %	17 (12–22)	57 (43–68)
Intrahepatic progression-free survival at 24 months, %	5 (2–8)	15 (7–25)
Median extrahepatic progression-free survival, months	4 (3–5)	12 (7–15)
Extrahepatic progression-free survival at 12 months, %	16 (11–21)	48 (35–59)
Extrahepatic progression-free survival at 24 months, %	3 (1–6)	15 (7–25)
Following radiotherapy initiation		
Median local control, months	–	Not reached*
Local control at 12 months, %	–	68 (50–81)
Local control at 24 months, %	–	52 (31–70)
Median intrahepatic progression-free survival, months	–	6 (4–9)
Intrahepatic progression-free survival at 12 months, %	–	30 (17–43)
Intrahepatic progression-free survival at 24 months, %	–	16 (7–29)
Median extrahepatic progression-free survival, months	–	4 (3–6)
Extrahepatic progression-free survival at 12 months, %	–	24 (14–36)
Extrahepatic progression-free survival at 24 months, %	–	14 (6–26)

*Discordance due to local progression events prior to initiation of L-RT.

effective in mitigating TRLF, promoting durable LC, and prolonging OS [4–6]. Limited evidence from registry data suggests that use of liver-directed local therapy for patients with metastatic ICC (M1) may be associated with longer OS [8]. To our knowledge, the current study is the first report describing outcomes with definitive L-RT in addition to chemotherapy in patients with M1 ICC (specifically, extrahepatic metastasis) in the contemporary era. Through the present study, we demonstrated that the use of L-RT is associated with higher LC and longer OS and less frequently associated with TRLF versus chemotherapy alone. Additionally, we showed that patients receiving L-RT had prolonged survival regardless of response to initial chemotherapy, suggesting that local therapy may alter the natural disease course of M1 ICC. Furthermore, we showed that patients who eventually expire from TRLF do so significantly later when treated with L-RT versus chemotherapy alone. Similar results were seen when OS for our institutional L-RT cohort was compared against patients in the NCDB receiving chemotherapy alone. Taken together, these findings suggest a novel role for L-RT in appropriately selected patients who initially present with M1 disease. An infographic of key conclusions from this study is shown in Figure 4.

Primary site-directed RT for the treatment of metastatic cancer has been shown to prolong survival for several disease sites, including low-volume metastatic prostate cancer [18] and nasopharyngeal cancer [19]. One possible rationale for primary site treatment has been the eradication of subclones with metastatic potential [20], thereby leading to reduced systemic burden of disease. While this mechanism may play a role in patients with M1 ICC, the more intriguing rationale for local therapy for M1 ICC is the mitigation of TRLF, which has been well described in several antecedent studies of locoregional ICC [5, 7, 16, 21]. Our results reaffirm the importance of LC of the primary and/or dominant liver lesion(s) with L-RT as a conduit to both deferring and decreasing rates of local progression, TRLF, and death.

When compared with patients receiving chemotherapy alone, patients receiving L-RT had lower rates of death due to TRLF but higher rates of death due to peritoneal or lung disease, typically later in the disease course (Fig. 2). A plausible explanation for this

Table 3. Univariate and multivariable Cox analyses for factors associated with overall survival following diagnosis

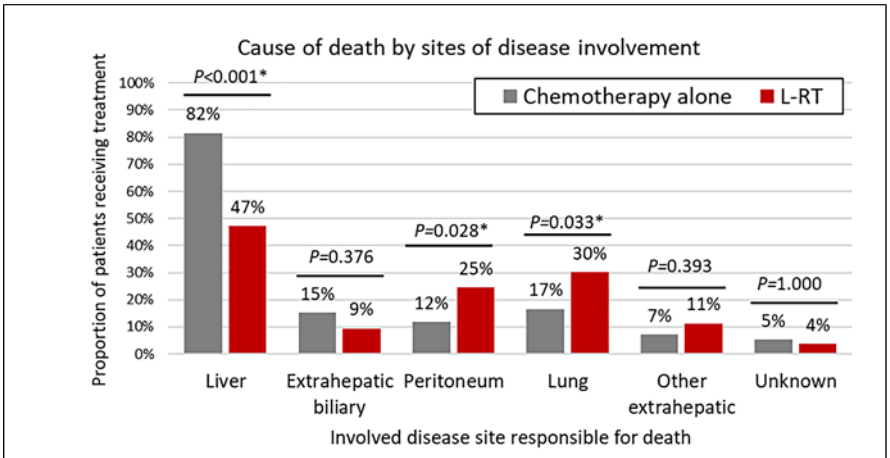
	Univariate Cox regression			Multivariable Cox regression		
Attribute	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Age at diagnosis, years	1.01	1.00–1.02	0.020*	1.01	1.00–1.02	0.026*
Sex						
Male	(Reference)					
Female	0.81	0.63–1.03	0.091			
ECOG performance status						
0–1	(Reference)			(Reference)		
2–3	2.29	1.63–3.22	<0.001*	2.01	1.38–2.91	<0.001*
CA 19–9, U/mL	1.000005	1.000001–1.000009	0.009*	1.000002	0.999998–1.000006	0.453
Maximal tumor size, cm	1.02	0.99–1.05	0.268			
T-stage						
1–2	(Reference)					
3–4	1.25	0.94–1.68	0.117			
N stage						
0	(Reference)					
1	1.20	0.85–1.68	0.299			
Non-regional nodal mets at diagnosis	1.21	0.95–1.55	0.125			
Peritoneal mets at diagnosis	1.23	0.95–1.58	0.114			
Osseous mets at diagnosis	1.10	0.85–1.44	0.465			
Lung mets at diagnosis	1.05	0.82–1.34	0.708			
Portal vein thrombus	0.97	0.68–1.39	0.889			
Satellitosis	0.97	0.75–1.26	0.831			
Chemotherapy duration, months	0.85	0.81–0.89	<0.001*	0.85	0.81–1.89	<0.001*
Treatment stratum						
Chemotherapy alone	(Reference)			(Reference)		
Chemotherapy + L-RT	0.45	0.33–0.62	<0.001*	0.41	0.30–0.56	<0.001*
RT pts only: RT BED_{10}	1.01	0.99–1.02	0.306			
RT pts only: ablative BED_{10}	0.86	0.47–1.60	0.640			

A threshold of $p < 0.05$ on univariate analysis was used for variable selection into the multivariable model. *Significant at 5% level.

phenomenon is that RT to the dominant liver lesion may alter the natural history of disease for M1 ICC to be preferentially skewed toward distant progression. Though early death due to TRLF is less common among patients receiving L-RT, these patients nevertheless may go on to succumb eventually to distant disease, a competing risk for death due to TRLF. Molecularly targeted systemic therapies and metastasis-directed local therapies may have a role in addressing these sites of distant progression and may warrant investigation in patients with stable liver disease following chemotherapy initiation.

Despite the fact that patients with M1 disease at diagnosis account for 20–30% of all cases of ICC, literature regarding the prognosis and optimal treatment of these patients is sparse. A study of the NCDB showed that patients with M1 ICC receiving liver-directed local therapies – a minority (27%) of whom received L-RT – had longer OS than those receiving chemotherapy alone [8]. The authors found that median OS was 8.3 months for patients receiving chemotherapy alone versus 16.7 months for those receiving chemotherapy followed by liver-directed local therapies, similar to our reported medians of 9 and 21 months, respectively. The authors also found that the presence of lung or bone metastases at diagnosis portended poorer outcomes, though we did not reproduce these findings with the cohorts in the present study. Another study using the Surveillance, Epidemiology, and End Results (SEER) database similarly showed that patients receiving local treatment of the primary tumor appeared to have longer survival; however, this study included patients with AJCC 7th edition N1 or M1 disease, and local therapies were primarily surgical resection or other local destruction procedures [22].

We must acknowledge the limitations of our research, the most pertinent of which is the retrospective design with potential selection bias, which we made attempts to mitigate, including landmark analyses, propensity score matching, and a matched comparison with patients from a large cancer registry. A subset of patients treated with chemotherapy are likely poor candidates for L-RT given the presence of diffuse metastases precluding safe treatment with



	Median (95% CI) survival stratified by cause of death and treatment cohort, months					
	Liver	Extrahepatic biliary	Peritoneum	Lung	Other extrahepatic	Unknown
Chemo	9 (8-10)	9 (6-13)	9 (7-17)	15 (11-19)	8 (3-13)	10 (3-19)
L-RT	18 (16-25)	31 (18-undef)	18 (14-26)	17 (14-20)	9 (8-undef)	26 (26-undef)
P-value (log-rank)	0.0019*	0.0460*	0.1238	0.6531	0.9994	0.0608

Fig. 2. Comparison of suspected causes of death for patients treated with chemotherapy alone versus with L-RT. Percentages may sum to >100% as a result of multiple likely causes of death for a given patient. The associated table shows time to death stratified by responsible disease site and treatment cohort.

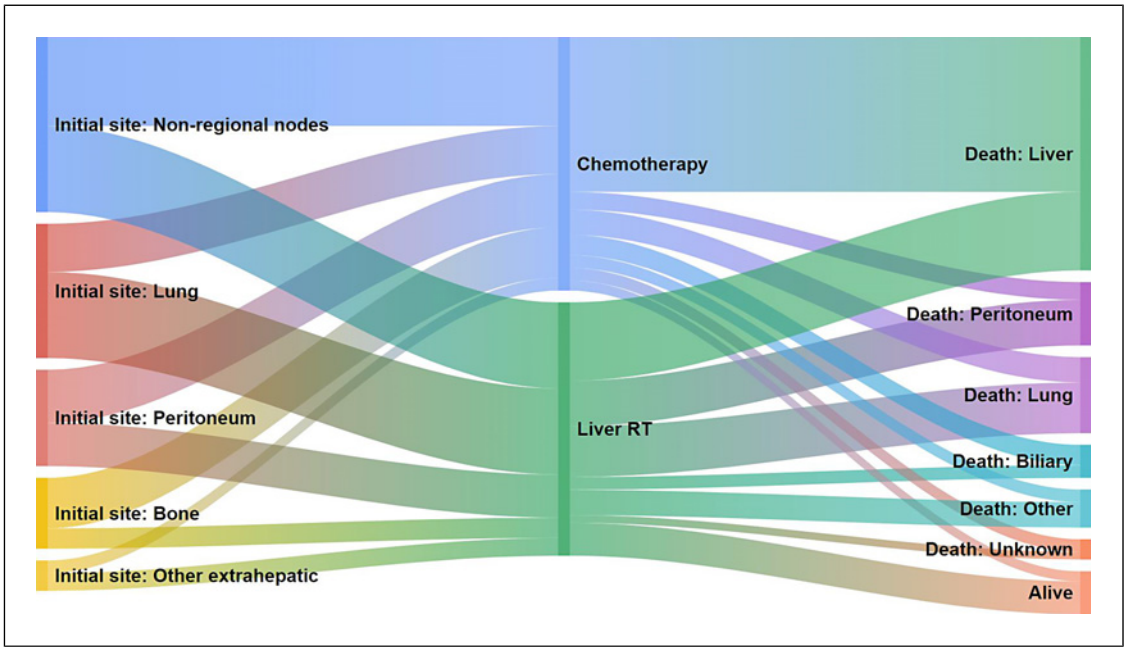


Fig. 3. Sites of initial metastatic disease involvement and causes of death for patients treated with chemotherapy alone and liver RT. The thickness of each segment is proportional to the relative frequency with respect to treatment cohort. For cases in which multiple sites of initial disease were identified for a patient, sites were equally weighted (e.g., in cases of two sites of disease, each site was weighted as 0.5). Similarly, for cases in which multiple likely causes of death were identified for a patient, causes were equally weighted.

RT. Also, given that this is a cohort of patients largely treated with systemic therapy, some patients elected to continue their systemic therapy closer to home and were lost to imaging/disease endpoint follow-up, potentially weakening our ability to make more precise conclusions about disease progression and cause of death. Heterogeneity in the specific

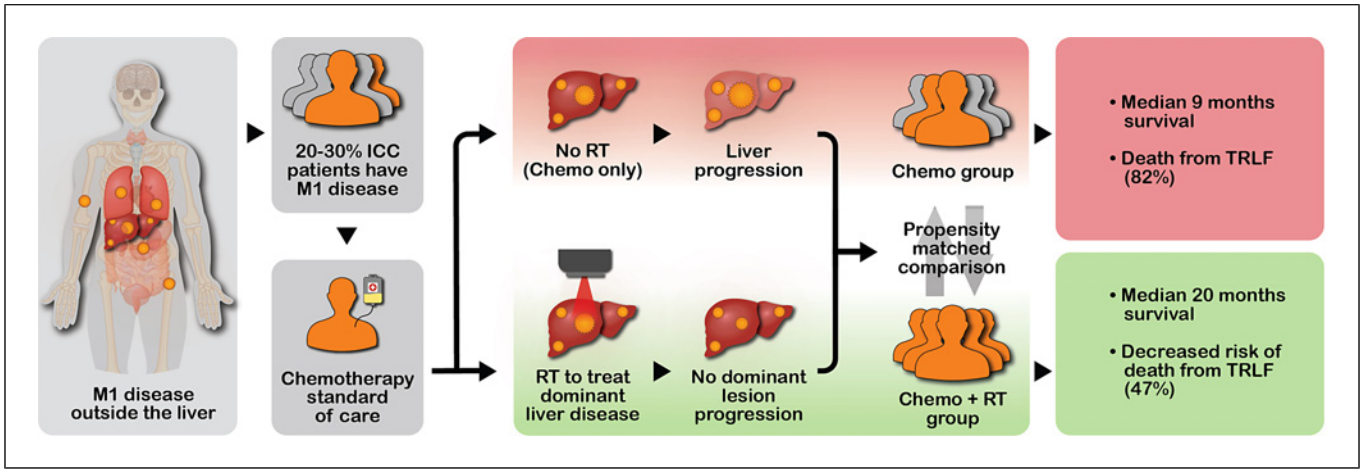


Fig. 4. Infographic of key conclusions of this study.

chemotherapy agents, duration of treatment, time from diagnosis to L-RT, L-RT dose, fractionation, and modality used also limited our ability to transcend mere association.

Despite the limitations of the current study, our results support the idea that L-RT may be considered in carefully selected patients with M1 ICC, with the primary goal of achieving LC of the dominant liver disease and mitigating TRLF as means to achieving longer survival. Future prospective and randomized studies are warranted to confirm these findings.

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Statement of Ethics

This study protocol was reviewed and approved by the MD Anderson Institutional Review Board, approval number PA14-0646. The requirement for informed consent was waived.

Conflict of Interest Statement

BD reports consulting honoraria from Sermo Inc. EBH reports research funding from Merck Serono. CT reports a consulting/advisory role with Accuray. EJK reports grants from National Institutes of Health, Stand Up 2 Cancer, MD Anderson Cancer Center, Philips Healthcare, Elekta, and GE Healthcare; personal fees from RenovoRx and Taylor and Francis; and a consulting/advisory role with Augmenix. ACK reports ownership of shares in Aravive, Inc. PD reports consulting/advisory relationships with the American Society for Radiation Oncology and the National Cancer Institute. All reported conflicts are outside of the submitted work.

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Author Contributions

Conception or design of the work, and drafting the article: De, Upadhyay, Koay, and Ludmir. Data collection: De, Upadhyay, Kumala, Shi, Dodoo, Abi and Jaoude. Data analysis and interpretation, critical revision of the article, and final approval of the version to be published: De, Upadhyay, Liao, Kumala, Shi, Dodoo, Abi Jaoude, Corrigan, Manzar, Marqueen, Bernard, S. Lee, Raghav, Vauthey, Tzeng, Tran Cao, G. Lee, Wo, Hong, Crane, Minsky, Smith, Holliday, Taniguchi, Koong, Das, Javle, Ludmir, and Koay.

Data Availability Statement

Data generated or analyzed during this study are included in this article and its online supplementary material. Further data that support the findings of this study are available upon reasonable request within 1 year of publication. Inquiries can be directed to the corresponding authors, EBL and EJK.

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