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Impact of liver-directed therapy in colorectal cancer liver metastases

Gabriela M. Vargas, MD, MS,[a,*] Abhishek D. Parmar, MD, MS,[a,b] Kristin M. Sheffield, PhD,[a] Nina P. Tamirisa, MD,[a,b] Kimberly M. Brown, MD,[a] and Taylor S. Riall, MD, PhD[a]

[a] Department of Surgery, The University of Texas Medical Branch, Galveston, Texas
[b] Department of Surgery, The University of California, Oakland, California

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ABSTRACT

Background: There is a paucity of data on the current management and outcomes of liver-directed therapy (LDT) in older patients presenting with stage IV colorectal cancer (CRC). The aim of the study was to evaluate treatment patterns and outcomes in use of LDT in the setting of improved chemotherapy.

Methods: We used Cancer Registry and linked Medicare claims to identify patients aged ≥66 y undergoing surgical resection of the primary tumor and chemotherapy after presenting with stage IV CRC (2001–2007). LDT was defined as liver resection and/or ablation-embolization.

Results: We identified 5500 patients. LDT was used in 34.9% of patients; liver resection was performed in 1686 patients (30.7%), and ablation-embolization in 554 patients (10.1%), with 322 patients having both resection and ablation-embolization. Use of LDT was negatively associated with increasing year of diagnosis (odds ratio [OR] = 0.96, 95% confidence interval [CI] 0.93–0.99), age >85 y (OR = 0.61, 95% CI 0.45–0.82), and poor tumor differentiation (OR = 0.73, 95% CI 0.64–0.83). LDT was associated with improved survival (median 28.4 *versus* 21.1 mo, $P < 0.0001$); however, survival improved for all patients over time. We found a significant interaction between LDT and period of diagnosis and noted a greater survival improvement with LDT for those diagnosed in the late (2005–2007) period.

Conclusions: Older patients with stage IV CRC are experiencing improved survival over time, independent of age, comorbidity, and use of LDT. However, many older patients deemed to be appropriate candidates for resection of the primary tumor and receipt of systemic chemotherapy did not receive LDT. Our data suggest that improved patient selection may be positively impacting outcomes. Early referral and optimal selection of patients for LDT has the potential to further improve survival in older patients presenting with advanced colorectal cancer.

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1. Introduction

Metastatic disease is present at the time of diagnosis in 20% of patients presenting with colorectal cancer (CRC), and for these patients, the liver is the most common site of metastatic disease [1,2]. Advances in chemotherapeutic regimens, surgical technique, and postoperative care have allowed for aggressive treatment of liver metastases in patients who

* *Corresponding author*. Department of Surgery, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555-0541. Tel.: +1 409 772 1836; fax: +1 409 747 2253.
E-mail address: gavargas@utmb.edu (G.M. Vargas).
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previously would have only been candidates for palliative chemotherapy. Liver resection is the only potentially curative option and the preferred treatment modality in patients with isolated and resectable liver metastases. However, resection may not be possible in the case of multiple metastases, extensive bilobar disease, or in patients who are poor surgical candidates. When resection is not possible, liver ablation or chemoembolization are alternative techniques to decrease tumor burden and prolong survival [3]. Treatment with aggressive multimodality therapy has led to 5-y survival rates exceeding 50% for select patients [4].

There is a paucity of data on the current management and outcomes in older patients presenting with CRC liver metastases. In the setting of metastatic disease at presentation, the management of liver metastases is especially challenging and the benefit of liver-directed therapy (LDT) in the setting of modern chemotherapy is not as clear. Although single institution retrospective studies from specialized centers have demonstrated low mortality rates in carefully selected older patients undergoing liver resection [5–12], these reports have included both synchronous and metachronous disease. In addition, the effects of ablative therapies such as radiofrequency ablation and chemoembolization on survival have not been well studied.

We used population-based data to evaluate the use of liver resection, ablation, and chemoembolization (LDT) in older patients presenting with metastatic CRC in the era of more effective oxaliplatin- and irinotecan-containing chemotherapeutic regimens [13–15]. We specifically evaluated time trends in the use of these modalities and, when used, the timing of LDT in relation to treatment of the primary tumor and receipt of systemic therapy. Finally, we evaluated the effects of these therapies on long-term survival.

2. Methods

This study was deemed to be exempt from review by the Institutional Review Board at the University of Texas Medical Branch.

2.1. *Data source*

We used Texas Cancer Registry (TCR)- and Surveillance Epidemiology and End Results (SEER)-linked Medicare data from 2000–2009. SEER and TCR collect data on all cancer cases covered by the respective registries. Data collected include patient demographics, primary tumor site, stage, first course of treatment, tumor morphology, cause of death, and survival [16,17]. All cancer-related variables included in the analysis were identical between the two registries. The Center for Medicare and Medicaid Services performed the Medicare linkage for both data sets. Approximately 98% of all people aged ≥65 y in TCR and 93% in SEER can be linked with Medicare enrollment and claims files [18,19]. The Medicare claims data include billing information on hospital stays, physician services, and hospital outpatient visits [20]. For this study, data were extracted from the Medicare Denominator file (demographics and eligibility), the Medicare Provider Analysis and Review file (MEDPAR, inpatient claims), the Carrier claim file (claims from noninstitutional service providers), and the

Table 1 – ICD-9 diagnosis codes used to identify CRC and treatment in patients presenting with stage IV CRC.

Cancer	ICD-O-3 histology codes
Adenocarcinoma	8000, 8050, 8051, 8052, 8010, 8021, 8022, 8140, 8141, 8143, 8145, 8147, 8210, 8211, 8220, 8221, 8230, 8260, 8261, 8262, 8263, 8430, 8440, 8470, 8471, 8480, 8481, 8490, 8550, 8551, 8570, 8571, 8572, 8573, 8574, and 8575
Treatment	**Procedure codes**
Colorectal resections	ICD-9-CM: 45.71-45.76, 45.79, 45.81-45.83, 17.31-17.36, 17.39, 48.42-48.43, 48.49-48.52, 48.59-48.64, 48.69 CPT: 44140-44141, 44143-44147, 44150-44153, 44160, 44204-44208, 44210, 44155-44158, 45110-45114, 45116, 45119-45121, 45123, 45126, 45160, 45170, 45171, 45172, 44120-44212, 45395, 45397
Chemotherapy	ICD-9 procedure code: 99.25 ICD-9 diagnosis codes: version 58.1, version 66.2, and version 67.2 HCPCS and CPT codes: Q0083-q0085, 51,720, J0640, 964XX, 96,400–96,549, J9000-J9999, G0355-G0363, G9021-G9032
Modern chemotherapy (oxaliplatin, irinotecan, or bevacizumab containing regimens)	J9263, J9206, and J9035
Standard chemotherapy (5-FU/LV only)	J9190 and J0640
Liver resections	CPT: 47100, 47120, 47122, 47125, 47130 ICD-9 codes: 50.12, 50.2, 50.22, 50.3
Ablation-embolization liver procedures	CPT: 47370 (RFA), 47371 (cryosurgical), 47380 (open RFA), 47381 (open cryosurgical), 47382 (percutaneous RFA) ICD-9: 50.2, 50.23-50.26, 50.29
Liver chemoembolization	CPT: 37204 and 75894 ICD-9: 50.93-50.94

5-FU = 5-Fluorouracil; LV = leucovorin.

Outpatient Standard Analytical File (claims from institutional outpatient providers) [20].

2.2. Cohort selection

We selected patients diagnosed with stage IV colon and rectal cancers and *International Classification of Diseases for Oncology*, third edition histology codes (Table 1) consistent with adenocarcinoma diagnosed between 2001 and 2007. We excluded patients who did not have Medicare Parts A and B coverage without Health Maintenance Organization for 1 y before and 2 y after diagnosis to allow for the evaluation of comorbidity in the year before diagnosis and to follow all patients for at least 2 y. Follow-up was complete in both data sets through the end of 2009. Finally, we excluded patients who did not undergo resection of the primary tumor and did not receive chemotherapy at any point after diagnosis, as liver resection is generally not indicated if the primary tumor is not optimally treated. Resection of the primary tumor and chemotherapy were included if they occurred before or after LDT. A total of 5500 patients met our inclusion criteria (Fig. 1).

2.3. Resection of primary tumor, chemotherapy, and LDT

Treatment of the primary tumor was defined as the receipt of chemotherapy and resection of the primary tumor after a diagnosis of stage IV CRC. Definitive resection of the primary tumor was identified from the Medicare claims (MEDPAR, carrier, and outpatient SAF) using International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM) procedure codes and Current Procedural Terminology, Fourth Edition (CPT-4) codes for colorectal resection (Table 1), including open and laparoscopic colon and rectal resections, with or without colostomy.

As defined on the SEER-Medicare website, we used MEDPAR, carrier, and outpatient claims to identify ICD-9, CPT/Healthcare Common Procedure Coding System codes, J codes, and revenue center codes for the administration of chemotherapy [21]. Specific regimens were identified by J codes for specific agents (Table 1). "Standard" chemotherapy was defined as 5-fluorouracil ± leucovorin. "Modern" chemotherapy was defined as any regimen containing oxaliplatin or irinotecan. Use of bevacizumab was analyzed independently. Patients were considered to have received chemotherapy if they had any of the codes listed in Table 1 at any point before or after surgical resection of the primary tumor.

Medicare claims in inpatient, outpatient, and carrier files were examined for ICD-9 or CPT procedure codes indicating receipt of LDT. LDT was defined as liver resection, liver ablation, or chemoembolization (Table 1). Few patients underwent ablation or chemoembolization; therefore, these categories were combined as "ablation-embolization" for all analyses.

2.4. Covariates

Patient characteristics included age, sex, race (white, black, Hispanic, and other), and the Klabunde modification of the Charlson comorbidity index (0, 1, 2, and ≥3) [22]. Median income and percent of residents with <12 y education were determined at the zip code level. Tumor characteristics included type (colon *versus* rectum), site (right, left, transverse, and rectum), nodal status, and tumor differentiation. All patients had stage IV disease at the time of diagnosis.

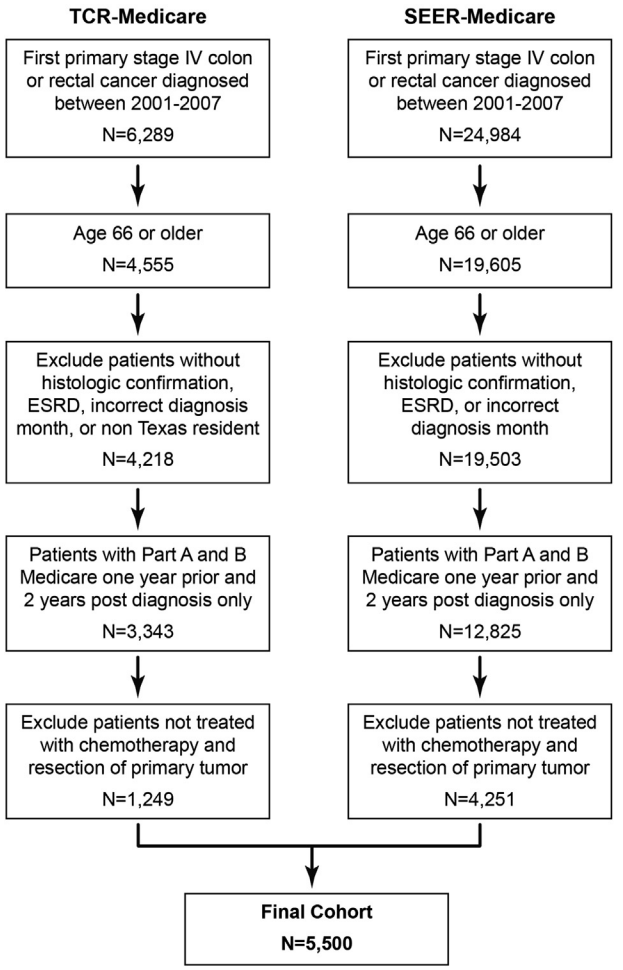

Fig. 1 – Cohort selection. TCR- and SEER-Medicare linked data for patients presenting with stage IV CRC. Patients who did not have Medicare parts A and B coverage without Health Maintenance Organization for 1 y before and 2 y after diagnosis were excluded. Only patients undergoing resection of the primary tumor and chemotherapy were included. The final cohort included 5500 patients.

2.5. Statistical analysis

We calculated summary statistics for the overall cohort and determined the percentage of patients receiving LDT. Chi-square tests were used to evaluate the unadjusted associations between LDT and patient, tumor, and primary treatment characteristics.

We used a Cochran–Armitage test for trend to evaluate trends in use of liver resection and liver ablation-embolization procedures. Multivariable logistic regression was used to determine factors independently associated with the receipt of LDT. Kaplan–Meier disease-specific 5-y survival curves were generated from date of diagnosis for patients in the following

Table 2 – Summary of overall cohort and bivariate analysis of factors associated with receipt of any LDT and liver resection in older adults with stage IV CRC.

Factor (*P* value)	Overall cohort $n = 5500$ (% of overall cohort)	LDT $n = 1918$ (% receiving LDT)	Liver resection $n = 1686$ (% receiving liver resection)
Gender			
Female	2758 (50.2)	909 (33.0)	797 (28.9)
Age, y (mean)[*,†]	74.3 ± 5.7	73.8 ± 5.5	73.7 ± 5.5
66–69	1339 (24.4)	516 (38.5)	452 (33.8)
70–74	1653 (30.1)	611 (37.0)	547 (33.1)
75–79	1430 (26.0)	489 (34.2)	425 (29.7)
80–84	789 (14.3)	229 (29.0)	202 (25.6)
≥85	289 (5.2)	73 (25.3)	60 (20.8)
Race			
White	4666 (84.9)	1648 (35.3)	1449 (31.1)
Black	479 (8.7)	163 (34.0)	144 (30.1)
Other	350 (6.4)	107 (30.6)	93 (26.5)
Charlson comorbidity index			
0	3522 (64.0)	1220 (34.6)	1071 (30.4)
1	1309 (23.8)	457 (34.9)	400 (30.6)
2	428 (7.8)	156 (36.4)	141 (32.9)
≥3	241 (4.4)	85 (35.3)	74 (30.7)
Cancer type			
Colon	4532 (82.4)	1561 (34.4)	1386 (30.6)
Rectum	968 (17.6)	357 (36.9)	300 (31.0)
Poorly differentiated tumors	1611 (29.3)	488 (30.3)	433 (26.9)
Emergency surgery			
Yes	1109 (20.2)	368 (33.2)	335 (30.2)
No	4391 (79.8)	1550 (35.3)	1351 (30.8)
Chemotherapy[*,†]			
Standard	1599 (29.1)	478 (29.9)	427 (26.7)
Modern	3123 (56.8)	1197 (38.3)	1050 (33.6)
Other	778 (14.2)	243 (31.2)	209 (26.9)
Bevacizumab[*,†]			
Yes	1535 (27.9)	602 (39.2)	514 (33.5)
LDT			
Resection	1686 (30.7)	NA	NA
Ablation-embolization	554 (10.1)	NA	NA
Period[†]			
2001–2004	3313 (60.2)	1173 (35.4)	1052 (31.8)
2005–2007	2187 (39.8)	745 (34.1)	634 (29.0)

P values for χ^2 analysis representing any difference within categories.
[*] Denotes $P < 0.0001$ for LDT.
[†] Denotes $P \leq 0.030$ for liver resection.

treatment groups: overall cohort, patients undergoing LDT, and those not treated with LDT. Log-rank tests were performed to compare survival in patients treated with LDT *versus* those not treated with LDT. This analysis was also stratified by time period (early = 2001–2004 and late = 2005–2007). A Cox proportional hazards model was used to evaluate the independent association between LDT and survival, as well as the interaction between period of diagnosis and LDT.

All *P* values were from two-sided tests. All analyses were performed with SAS version 9.2 (SAS Inc, Cary, NC). Statistical significance was accepted at the $P < 0.05$ level.

3. Results

3.1. *Patient and tumor characteristics*

We identified 5500 patients who received chemotherapy and underwent resection of the primary tumor (Fig. 1). The mean age of the cohort was 74.3 ± 5.7 y. Women comprised 50.2% of the study sample. The majority of patients were white and had a Charlson comorbidity score of zero. The primary tumor was of colonic origin in 82.4% of patients. (Table 2)

Per the selection criteria, all patients underwent surgical resection of the primary tumor and received chemotherapy. Surgical resection was performed in an emergent setting in 20.2% of patients. Modern oxaliplatin- or irinotecan-containing chemotherapy regimens were used in 56.8% of patients. Standard chemotherapy (5-fluorouracil and leucovorin) was administered to 29.0% of patients. The remaining 14.2% of patients received other agents. Bevacizumab was used in 27.9% of patients (Table 2).

LDT, defined as liver resection or ablation-embolization, was performed in 1918 patients (34.9%). Liver resection was performed in 1686 patients over the course of the study period. Of these, 1289 had one or more biopsy or wedge resections, 174 had one or more lobectomies, 108 had one or more partial hepatectomies, and 115 had a combination of any of the

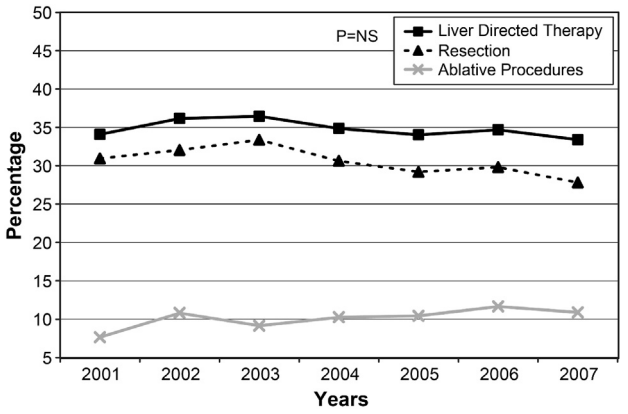

Fig. 2 – Time trends in use of LDT. Rates of LDT remained stable over time (34.1% in 2001 *versus* 33.4% in 2007, P = NS).

procedures. Of the 115 patients having more than one type of resection, 96 had a biopsy or wedge and either a lobectomy or partial hepatectomy. The remaining 19 patients had lobectomy and partial hepatectomy. Ablation-embolization was performed in 554 patients (10.1%). Of these patients, 322 were treated with both resection and some form of ablation-embolization. Liver resection rates were stable over time (31.0% in 2001 to 27.8% in 2007, P = Not Significant, Fig. 2) as were rates of ablation-embolization (7.6% in 2001 to 10.9% in 2007, P = Not Significant, Fig. 2), but the use of modern chemotherapy increased from 41.0% in 2001 to 77.3% in 2007, $P < 0.0001$.

The mean time from diagnosis to LDT was 117 ± 217 d. Patients undergoing liver resection underwent resection a mean of 83 ± 168 d after diagnosis; whereas, patients undergoing ablation-embolization had a mean time of 390 ± 371 d between diagnosis and ablation or chemoembolization. LDT was performed at the time of resection of the primary tumor in 74.4%, after resection in 21.2%, and before resection in 4.5%. In 76.0% of patients, LDT and resection of the primary tumor were performed before the administration of systemic chemotherapy. LDT and primary tumor resection were performed after chemotherapy in 7.4% and chemotherapy was administered between primary tumor resection and LDT in 16.6% of patients (Fig. 3).

3.2. *Factors associated with LDT*

In a bivariate analysis (Table 2), younger age, receipt of modern chemotherapy, and use of bevacizumab were associated with a higher likelihood of receiving LDT. Patients treated with ablation-chemoembolization were more likely to be younger and have colon primary tumors. In a multivariable model (Table 3) controlling for comorbidity and socioeconomic status, there was a negative association between use of LDT and increasing year of diagnosis (odds ratio [OR] = 0.96, 95% confidence interval [CI] 0.93–0.99), age >85 y (OR = 0.61, 95% CI 0.45–0.82), and poor tumor differentiation (OR = 0.73, 95% CI 0.64–0.83). The administration of modern chemotherapy was more strongly associated with LDT use than treatment with standard chemotherapeutic regimens (OR = 1.44, 95% CI 1.25–1.66).

3.3. *LDT and survival*

The median disease-specific survival for the overall cohort was 23.4 mo. When stratified by treatment of liver metastases, the median survival was 28.4 mo for patients undergoing LDT compared with 21.1 mo in patients who did not receive treatment for liver metastases ($P < 0.0001$, Fig. 4). However, survival improved for both groups over time. When stratified by period of diagnosis, there was an improvement in median survival from 25.4 mo in the early period (2001–2004) to

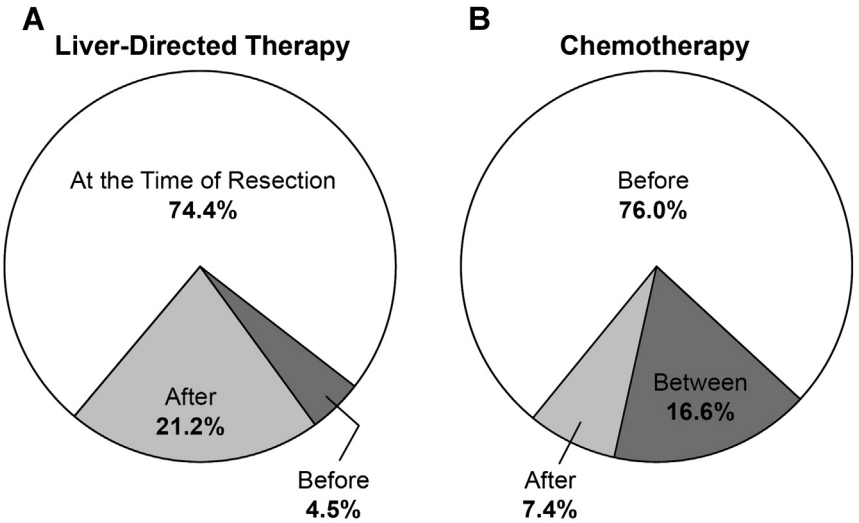

Fig. 3 – Timing of LDT in relation to treatment of the primary tumor in patients undergoing treatment of liver metastases. (A) Timing of LDT relative to resection of the primary tumor. At the time of primary tumor resection, 74.4% of patients underwent LDT. (B) Timing of chemotherapy relative to resection of the primary tumor and LDT. Chemotherapy was the initial treatment modality in 76.0% of patients. Chemotherapy was given to 16.6% of patients between resection of the primary tumor and LDT.

Table 3 – Multivariate analysis of factors associated with LDT in patients with stage IV CRC.

Factor (REF)	Odds ratio	Confidence interval
Year of diagnosis	0.96	0.93–0.99
Age, y (66–69)		
70–74	0.94	0.81–1.10
75–79	0.87	0.74–1.02
80–84	0.71	0.89–0.87
≥85	0.61	0.45–0.82
Sex (female)	1.13	1.00–1.26
Race (white)		
Black	0.96	0.78–1.18
Hispanic	0.89	0.58–1.35
Other	0.74	0.56–0.99
Cancer (rectum)	0.88	0.58–1.35
Poorly differentiated (no)	0.73	0.64–0.83
Charlson comorbidity (0)		
1	1.05	0.92–1.20
2	1.13	0.91–1.39
≥3	1.18	0.89–1.56
Node status (positive)		
Negative	1.02	0.88–1.18
Unknown	0.59	0.48–0.74
Income (Q1)		
Q2	1.03	0.87–1.22
Q3	0.98	0.83–1.15
Q4	1.14	0.97–1.35
Surgery (elective)	0.94	0.82–1.09
Chemotherapy (standard)		
Modern	1.44	1.25–1.66
Other	1.11	0.92–1.35

REF = reference.

35.9 mo in the late period (2005–2007) in patients undergoing LDT ($P < 0.0001$). Similarly, for patients not treated with LDT, median survival improved from 19.6 mo to 23.4 mo between the early and late periods ($P < 0.0001$, Fig. 5).

In a Cox proportional hazards model, there was a significant interaction between receipt of LDT and period of diagnosis ($P = 0.04$). Therefore, the analysis was stratified by period of diagnosis. Receipt of LDT in the later period was associated with a 25% decrease in the hazard of death compared with a 16% decrease in the early period (Table 4).

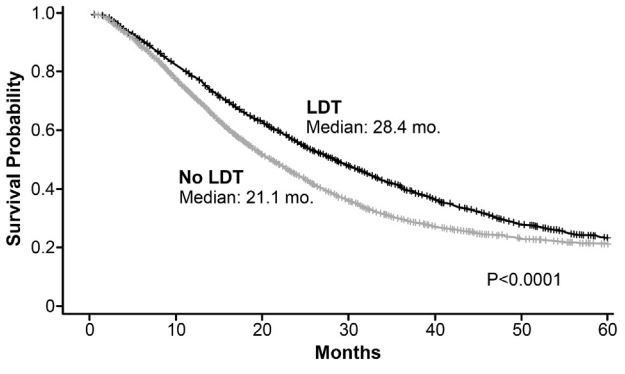

Fig. 4 – Kaplan–Meier analysis of the 5-y disease-specific survival for patients treated with resection of the primary tumor and chemotherapy stratified by receipt of LDT. Median survival was 28.4 mo for patients undergoing LDT compared with 21.1 mo in patients who did not receive treatment for liver metastases ($P < 0.0001$).

4. Discussion

Our data demonstrate that survival has significantly improved over time in older patients presenting with stage IV CRC. As expected, carefully selected patients treated with chemotherapy, resection of the primary tumor, and LDT experienced optimal 5-y disease-specific survival. However, our data suggest that many older patients deemed to be appropriate candidates for resection of the primary tumor and receipt of systemic chemotherapy did not receive LDT. All patients in this study underwent resection of the primary tumor, implying a reasonable performance status. In addition, the 40% 5-y disease-specific survival rate in the group not receiving LDT indicates that a large proportion of these patients may have been adequate candidates for LDT, both from the standpoint of operative risk and disease burden.

LDT use was stable over time in this older cohort with stage IV CRC and resected primary tumors, with the majority of LDT in this age group being wedge resections or minor liver procedures rather than formal lobectomies or partial hepatectomies. In addition, survival improved over time, independent of receipt of LDT or modern chemotherapy. Younger age was one of the three factors independently associated with receipt of LDT, consistent with previous studies demonstrating lower use of LDT, particularly liver resection, with increasing age [23–25]. In a population-based study evaluating referral patterns in patients with isolated CRC liver metastases, Ksienski *et al.* [26] found that age was the most common reason cited for nonreferral to a hepatobiliary surgeon. However, short- and long-term outcomes after liver resection in carefully selected older patients are no different than in their younger counterparts [6–12,27–29]. Similarly, in patients aged ≥ 70 y not eligible for hepatic resection, the use of arterial embolization with or without radiofrequency ablation has not been associated with worse short-term outcomes [30]. With advances in chemotherapeutic regimens, our data suggest that early referral and optimal selection of patients for LDT has the potential to further improve survival in older patients presenting with advanced CRC.

Our data contribute to the existing literature illustrating a marked improvement in survival over the last 2 decades for patients with stage IV CRC. Even after we controlled for receipt of LDT, period of diagnosis was independently associated with improved survival. Improvements in cancer survival over time have been previously documented using SEER data by Sun *et al.* [31] Likewise, using data from two high-volume cancer referral centers and SEER data from 1990–2005 to confirm the trends, Kopetz *et al.* [32] observed a survival improvement for patients with metastatic CRC over time. Survival for those diagnosed after 2004 was temporally related to the adoption of newer chemotherapeutic agents. The value of newer chemotherapeutic agents has also been observed in a previous population-based study [33]. The gains in survival over time are likely multifactorial and attributable in part to the rapid adoption of modern chemotherapeutic regimens, improvements in patient selection for surgery, and advances in the

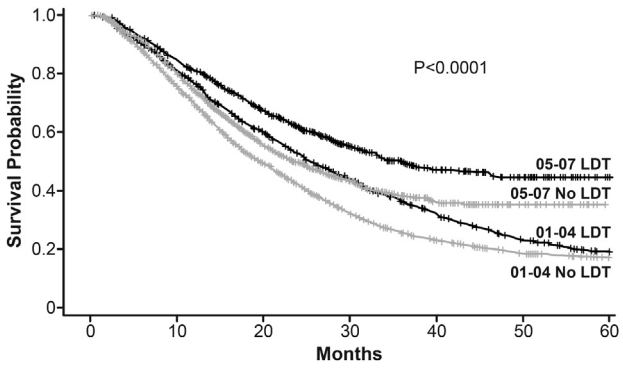

Fig. 5 – Kaplan–Meier analysis of the 5-y disease-specific survival for patients treated with resection of the primary tumor and chemotherapy ± LDT, stratified by early and late periods. Median survival improved over time, from 25.4–35.9 mo in patients undergoing LDT ($P < 0.0001$). Median survival also improved for patients who did not receive LDT (19.6 *versus* 23.4 months, $P < 0.0001$).

management of tumor-related complications [34]. In addition, it is established that CRC patients have improved survival when metastatic disease is identified early in the course of illness. The use of computed tomography in the work up of patients with CRC has proven to lead to the earlier detection of metastases and improved survival and may also account for the improved survival seen over time [35–37].

Our findings also support the concept that optimal selection for hepatic resection may improve outcomes, which has been previously introduced in other population-based studies. A retrospective review by Mala *et al.* [38] validated a preoperative clinical risk score to select patients who are most likely to benefit from hepatic resection of CRC metastases. Patients undergoing hepatic resection for CRC liver metastases were stratified into one of five clinical risk scores as defined by Fong *et al.* [39] Survival analysis of these patients demonstrated a statistically significant difference in survival for patients with a clinical risk score of 0–2 compared with patients with a clinical risk score of 3–4 ($P = 0.0006$). Multiple subsequent studies have since validated the clinical risk score as a viable tool to reduce postoperative morbidity and mortality through better patient selection [40,41]. Another study further emphasized enhanced urgency in applying this selection process specifically to older patients [6].

Our study has several limitations. Using observational data in cancer patients, there is a significant likelihood for selection bias in comparing patients undergoing different treatment regimens, especially when surgery is considered. Our cohort included only patients receiving combined treatment for CRC metastatic to the liver, making them a highly selected group of

Table 4 – Cox models for 5-y disease-specific survival for the overall cohort, in the early period (2001–2004) and late period (2005–2007).

Factor (REF)	Overall cohort	2001–2004 HR (95% CI)	2005–2007 HR (95% CI)
Treatment (LDT)	0.82 (0.76–0.88)	0.84 (0.77–0.91)	0.75 (0.66–0.86)
Period (2001–2004)	0.68 (0.63–0.73)	NA	NA
Age, y (66–69)			
70–74	1.13 (1.03–1.24)	1.09 (0.97–1.22)	1.20 (1.02–1.41)
75–79	1.23 (1.12–1.36)	1.20 (1.07–1.35)	1.28 (1.08–1.52)
80–84	1.40 (1.25–1.56)	1.37 (1.20–1.57)	1.46 (1.21–1.78)
≥85	1.66 (1.42–1.95)	1.80 (1.48–2.18)	1.35 (1.01–1.80)
Sex (female)	0.97 (0.91–1.03)	0.93 (0.86–1.00)	1.07 (0.95–1.20)
Race (white)			
Black	1.09 (0.97–1.23)	1.07 (0.93–1.24)	1.14 (0.92–1.41)
Hispanic	0.88 (0.69–1.12)	0.91 (0.69–1.20)	0.79 (0.47–1.32)
Other	0.94 (0.80–1.10)	0.94 (0.77–1.15)	0.94 (0.71–1.24)
Cancer (rectum)	1.21 (1.11–1.33)	1.17 (1.05–1.30)	1.35 (1.15–1.59)
Poorly differentiated (no)	1.37 (1.27–1.47)	1.33 (1.22–1.45)	1.45 (1.28–1.65)
Charlson comorbidity (0)			
1	1.01 (0.94–1.09)	1.00 (0.91–1.10)	1.00 (0.87–1.15)
2	1.15 (1.02–1.30)	1.14 (0.98–1.32)	1.18 (0.96–1.47)
≥3	1.10 (0.92–1.30)	1.34 (1.08–1.66)	0.81 (0.61–1.08)
Node status (positive)			
Negative	0.52 (0.47–0.57)	0.51 (0.46–0.57)	0.55 (0.46–0.66)
Unknown	0.99 (0.88–1.11)	0.96 (0.84–1.11)	1.05 (0.86–1.28)
Income (Q1)			
Q2	1.08 (0.98–1.19)	1.05 (0.93–1.18)	1.11 (0.93–1.31)
Q3	1.02 (0.92–1.12)	1.01 (0.90–1.14)	1.02 (0.86–1.21)
Q4	0.93 (0.84–1.02)	0.94 (0.83–1.05)	0.90 (0.75–1.07)
Chemotherapy (standard)			
Modern	1.13 (1.04–1.22)	1.26 (1.15–1.37)	0.81 (0.68–0.95)
Other	1.27 (1.15–1.41)	1.22 (0.07–1.38)	1.23 (1.00–1.51)

NA = not applicable; REF = reference.
Interaction between period and receipt of LDT $P = 0.04$.

patients. These patients likely had a higher functional status, were fit enough to tolerate aggressive cancer treatment, and their extent of metastatic disease was likely limited when compared with other patients with stage IV CRC. As a result, the validity of our study is limited to these patients only, and care should be taken when extrapolating these results to all CRC patients with synchronous liver metastases. Although patients who underwent LDT likely had a lower burden of disease, we are unable to assess the extent of disease present using administrative data. Nonetheless, we observed a survival improvement over time for all patients independent of treatment of liver metastases.

Older patients with stage IV CRC are experiencing improved survival over time independent of age, comorbidity, and use of LDT. However, many older patients deemed to be appropriate candidates for resection of the primary tumor and receipt of systemic chemotherapy are not receiving LDT. Improved patient selection and earlier detection of metastatic disease may be positively impacting outcomes. Early referral and optimal selection of patients for LDT has the potential to further improve survival in older patients presenting with advanced CRC. Patients presenting with stage IV CRC should be treated by a multidisciplinary team approach and practitioners should continue to incorporate patient and tumor factors in the selection criteria for the treatment of liver metastases.

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Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article

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