Published in final edited form as:
J Surg Res. 2014 September ; 191(1): 42–50. doi:10.1016/j.jss.2014.05.070.

Impact of Liver Directed Therapy in Colorectal Cancer Liver Metastases

Gabriela M. Vargas, MD, MS[1], **Abhishek D. Parmar, MD, MS**[1,2], **Kristin M. Sheffield, PhD**[1], **Nina P. Tamirisa, MD**[1,2], **Kimberly M. Brown, M.D.**[1], and **Taylor S. Riall, MD, PhD**[1]

[1]Departments of Surgery, The University of Texas Medical Branch, Galveston, Texas

[2]The University of California, San Francisco-East Bay, Oakland, California

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).

Objective—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 ≥66 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 ablative procedures.

Results—We identified 5,500 patients. LDT was used in 34.9% of patients; liver resection was performed in 1,686 patients (30.7%) and locoregional therapy 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 (OR=0.96, 95% CI 0.93–0.99), age >85 (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 vs. 21.1 months, P<0.0001); however, survival improved for all patients over time. We found a significant interaction between LDT and time period of diagnosis and noted a greater survival improvement with LDT for those diagnosed in the late (2005–2007) time period.

Conclusions—Older patients with stage IV CRC are experiencing improved survival over time independent of age, comorbidity and use of LDT. Greater gains in survival are seen with LDT for

Corresponding Author: Gabriela M. Vargas, MD, MS, Department of Surgery, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555-0541, Phone: 409-772-1836, Fax: 409-747-2253, gavargas@utmb.edu.

Author contributions:
Gabriela M. Vargas, MD, MS-Analysis and interpretation, writing the article, and critical revisions of the article.
Abhishek D. Parmar, MD, MS- Writing the article and critical revisions of the article.
Kristin M. Sheffield, PhD-Conseption, design, data interpretation, and writing the article.
Nina P. Tamirisa, MD- Writing the article and critical revisions of the article.
Kimberly M. Brown, M.D-Conception and design
Taylor S. Riall, MD, PhD-Conception, design, data analysis and interpretation, writing the article and critical revisions of the article.

patients diagnosed in the later time period. These data suggest that improved patient selection may be positively impacting outcomes.

Keywords

metastatic colorectal cancer; liver directed therapy; synchronous lesions; colorectal cancer liver metastases

INTRODUCTION

Metastatic disease is present at the time of diagnosis in 20% of patients presenting with colorectal cancer, 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 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-year 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 colorectal cancer 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 in the setting of modern chemotherapy is not as clear. While 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 (liver directed therapy) in older patients presenting with metastatic colorectal cancer (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 employed, the timing of liver directed therapy 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.

METHODS

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

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 datasets. Approximately 98% of all people aged 65 and older 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 non-institutional service providers), and the Outpatient Standard Analytical File (OutSAF, claims from institutional outpatient providers).[20]

Cohort Selection

We selected patients diagnosed with stage IV colon and rectal cancers and ICD-O-3 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 HMO for one-year prior and two years following diagnosis to allow for evaluation of comorbidity in the year prior to diagnosis and to follow all patients for at least two years. Follow-up was complete in both datasets 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 liver directed therapy. 5,500 patients met our inclusion criteria (Figure 1).

Resection of Primary Tumor, Chemotherapy, and Liver-Directed Therapy

Treatment of the primary tumor was defined as the receipt of chemotherapy and resection of the primary tumor after a diagnosis of stage IV colorectal cancer. Definitive resection of the primary tumor was identified from the Medicare claims (MEDPAR, carrier, 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 (HCPCS) codes, J codes, and revenue center codes for 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 liver directed therapy. Liver directed therapy 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.

Covariates

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

Statistical Analysis

We calculated summary statistics for the overall cohort and determined the percentage of patients receiving liver directed therapy. Chi square tests were used to evaluate the unadjusted associations between liver directed therapy 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 liver directed therapy. Kaplan-Meier disease-specific 5-year survival curves were generated from date of diagnosis for patients in the following treatment groups: overall cohort, patients undergoing liver directed therapy, and those not treated with liver directed therapy. Log rank tests were performed to compare survival in patients treated with liver directed therapy vs. those not treated with liver directed therapy. 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 liver directed therapy and survival, as well as the interaction between time period of diagnosis and liver directed therapy.

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

RESULTS

Patient and tumor characteristics (Table 2)

We identified 5,500 patients who received chemotherapy and underwent resection of the primary tumor (Figure 1). The mean age of the cohort was 74.3 ± 5.7 years. 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.

Treatment (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-FU 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).

Liver directed therapy, defined as liver resection or ablation/embolization, was performed in 1,918 (34.9%) patients. Liver resection was performed in 1,686 patients (30.7%). Liver resection was performed in 1,686 patients over the course of the study period. Of these, 1,289 had one or more biopsy/wedge resection, 174 had one or more lobectomies, 108 had one or more partial hepatectomies, and 115 had a combination of any of the procedures. Of the 115 patients having more than one type of resection, 96 had a biopsy/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=NS, Figure 2) as were rates of ablation/embolization (7.6% in 2001 to 10.9% in 2007, P=NS, Figure 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 liver directed therapy was 117 ± 217 days. Patients undergoing liver resection underwent liver resection a mean of 83 ± 168 days after diagnosis; whereas, patients undergoing ablation/embolization had a mean time of 390 ± 371 days between diagnosis and ablation or chemoembolization. Liver directed therapy 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, liver directed therapy and resection of the primary tumor were performed prior to administration of systemic chemotherapy. Liver directed therapy and primary tumor resection were performed after chemotherapy in 7.4% and chemotherapy was administered between primary tumor resection and liver directed therapy in 16.6% of patients (Figure 3).

Factors associated with liver directed therapy

In a bivariate analysis (Table 2), younger age, receipt of modern chemotherapy, and use of bevacizumab were associated with a higher likelihood of receiving liver directed therapy. 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 liver directed therapy and increasing year of diagnosis (OR=0.96, 95% CI 0.93–0.99), age >85 (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 liver directed therapy use than treatment with standard chemotherapeutic regimens (OR=1.44, 95% CI 1.25–1.66).

Liver directed therapy and survival

The median disease-specific survival for the overall cohort was 23.4 months. When stratified by treatment of liver metastases, the median survival was 28.4 months for patients undergoing liver-directed therapy compared to 21.1 months in patients who did not receive treatment for liver metastases (P<0.0001, Figure 4). However, survival improved for both groups over time. When stratified by time period of diagnosis, there was an improvement in median survival from 25.4 months in the early time period (2001-2004) to 35.9 months in the late time period (2005–2007) in patients undergoing liver directed therapy (P<0.0001). Similarly, for patients not treated with liver directed therapy, median survival improved from 19.6 months to 23.4 months between the early and late time periods (P<0.0001, Figure 5).

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

DISCUSSION

Our data demonstrate that survival has significantly improved over time in older patients presenting with stage IV colorectal cancer. As expected, carefully selected patients treated with chemotherapy, resection of the primary tumor, and liver directed therapy experienced optimal 5-year 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 liver directed therapy. All patients in this study underwent resection of the primary tumor, implying a reasonable performance status. In addition, the 40% five-year disease specific survival rate in the group not receiving liver directed therapy indicates that a large proportion of these patients may have been adequate candidates for liver directed therapy, both from the standpoint of operative risk and disease burden.

Liver directed therapy use was stable over time in this older cohort with stage IV colorectal cancer and resected primary tumors, with the majority of liver directed therapy 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 liver-directed therapy or modern chemotherapy. Younger age was one of three factors independently associated with receipt of liver directed therapy, consistent with previous studies demonstrating lower use of liver directed therapy, particularly liver resection, with increasing age.[23–25] In a population based study evaluating referral patterns in patients with isolated colorectal cancer liver metastases, Ksienski et al. found that age was the most common reason cited for non referral to a hepatobiliary surgeon.[26] However, short-term and long-term outcomes following liver resection in carefully selected older patients are no different than in their younger counterparts.[6–12, 27–29] Similarly, in patients ≥ 70 years old 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 liver directed therapy has the potential to further improve survival in older patients presenting with advanced colorectal cancer.

Our data contribute to the existing literature illustrating a marked improvement in survival over the last two decades for patients with stage IV colorectal cancer. Even after we controlled for receipt of liver-directed therapy, time 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. observed a survival improvement for patients with metastatic colorectal cancer over time. Survival for those diagnosed after 2004 was temporally related to the adoption of newer chemotherapeutic agents.[32] 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 multi-factorial and attributable in part to the rapid adoption of modern chemotherapeutic regimens, improvements in patient selection for surgery, and advances in the management of tumor related complications.[34] In addition, it is established that colorectal cancer 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 colorectal cancer 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. validated a preoperative clinical risk score to select patients who are most likely to benefit from hepatic resection of colorectal cancer metastases.[38] Patients undergoing hepatic resection for colorectal cancer 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 to 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 colorectal cancer metastatic to the liver, making them a highly selected group of 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 to other patients with stage IV colorectal cancer. 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 colorectal cancer patients with synchronous liver metastases. Although patients who underwent liver directed therapy 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 liver directed therapy. However, many older patients deemed to be appropriate candidates for resection of the primary tumor and receipt of systemic chemotherapy are not receiving liver directed therapy. Improved patient selection and earlier detection of metastatic disease may be positively impacting outcomes. Early referral and optimal selection of patients for liver directed therapy has the potential to further improve survival in older patients presenting with advanced colorectal cancer. Patients presenting with stage IV colorectal cancer should be treated by a multi-disciplinary team approach and practitioners should continue to incorporate patient and tumor factors in the selection criteria for treatment of liver metastases.

Acknowledgments

Funding: Supported by grants from the Cancer Prevention Research Institute of Texas Grant # #RP101207-P03, the UTMB Clinical and Translational Science Award #UL1TR000071, NIH T-32 Grant # 5T32DK007639, and AHRQ grant #1R24HS022134

Statement Regarding Texas Cancer Registry and SEER Data

The collection of cancer incident data used in this study was supported by the Texas Department of State Health Services and Cancer Prevention Research Institute of Texas, as part of the statewide cancer reporting program, and the Centers for Disease Control and Prevention's National Program of Cancer Registries Cooperative Agreement #5U58/DP000824-05. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the DSHS, CPRIT, or CDC. The collection of the California cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center, contract N01-PC-35139 awarded to the University of Southern California and contract N02-PC-15105 awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries under agreement No. U55/CCR921930-02 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred. The authors acknowledge the efforts of the Applied Research Program, NCI; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

References

1. Bouvier AM, Remontet L, Jougla E, et al. Incidence of gastrointestinal cancers in France. Gastroenterol Clin Biol. 2004; 28(10 Pt 1):877–81. [PubMed: 15523225]
2. Abdalla EK, Adam R, Bilchik AJ, et al. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006; 13(10):1271–80. [PubMed: 16955381]
3. Alsina J, Choti MA. Liver-directed therapies in colorectal cancer. Semin Oncol. 2011; 38(4):561–7. [PubMed: 21810515]
4. Tzeng CW, Aloia TA. Colorectal liver metastases. J Gastrointest Surg. 2013; 17(1):195–202. [PubMed: 23054896]
5. Anaya DA, Becker NS, Abraham NS. Global graying, colorectal cancer and liver metastasis: new implications for surgical management. Crit Rev Oncol Hematol. 2011; 77(2):100–8. [PubMed: 20206548]
6. Brand MI, Saclarides TJ, Dobson HD, et al. Liver resection for colorectal cancer: liver metastases in the aged. Am Surg. 2000; 66(4):412–5. discussion 415–6. [PubMed: 10776881]

7. Figueras J, Ramos E, López-Ben S, et al. Surgical treatment of liver metastases from colorectal carcinoma in elderly patients. When is it worthwhile? Clin Transl Oncol. 2007; 9(6):392–400. [PubMed: 17594954]
8. Mazzoni G, Tocchi A, Miccini M, et al. Surgical treatment of liver metastases from colorectal cancer in elderly patients. Int J Colorectal Dis. 2007; 22(1):77–83. [PubMed: 16538491]
9. Nagano Y, Nojiri K, Matsuo K, et al. The impact of advanced age on hepatic resection of colorectal liver metastases. J Am Coll Surg. 2005; 201(4):511–6. [PubMed: 16183488]
10. Nojiri K, Nagano Y, Tanaka K, et al. Validity of hepatic resection of colorectal liver metastases in the elderly (75 years and older). Anticancer Res. 2009; 29(2):583–8. [PubMed: 19331207]
11. Mann CD, Neal CP, Pattenden CJ, et al. Major resection of hepatic colorectal liver metastases in elderly patients - an aggressive approach is justified. Eur J Surg Oncol. 2008; 34(4):428–32. [PubMed: 17466484]
12. de Liguori Carino N, van Leeuwen BL, Ghaneh P, et al. Liver resection for colorectal liver metastases in older patients. Crit Rev Oncol Hematol. 2008; 67(3):273–8. [PubMed: 18595728]
13. Saltz LB, Cox JV, Blanke C, et al. Irinotecan Study Group. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med. 2000; 343(13):905–14. [PubMed: 11006366]
14. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000; 18(16):2938–47. [PubMed: 10944126]
15. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet. 2000; 355(9209):1041–7. [PubMed: 10744089]
16. Texas Cancer Registry. Available at: http://www.dshs.state.tx.us/tcr/
17. [Accessed March 22, 2013, 2013.] Surveillance Epidemiology and End Results (SEER). Available at: http://seer.cancer.gov/about/overview.html
18. Cancer Epidemiology and Surveillance Branch. Texas Department of State Health Services, Texas Cancer Registry Division; Available at: http://www.dshs.state.tx.us/tcr/default.shtm [Accessed 05/06/2013.]
19. National Cancer Institute. [Accessed 05/06/2013.] SEER-Medicare 2013. Available at: http://healthservices.cancer.gov/seermedicare/overview/linked.html
20. Research Data Assistance Center (ResDAC). Medicare Claims. Available at: http://www.resdac.org/cms-data/file-family/Medicare-Claims
21. [Accessed March 18, 2013, 2013.] Procedure codes for SEER-Medicare Analysis. Available at: http://healthservices.cancer.gov/seermedicare/considerations/procedure_codes.html
22. Klabunde CN, Legler JM, Warren JL, et al. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. Ann Epidemiol. 2007; 17(8):584–90. [PubMed: 17531502]
23. Cummings LC, Payes JD, Cooper GS. Survival after hepatic resection in metastatic colorectal cancer: a population-based study. Cancer. 2007; 109(4):718– 26. [PubMed: 17238180]
24. Temple LK, Hsieh L, Wong WD, et al. Use of surgery among elderly patients with stage IV colorectal cancer. J Clin Oncol. 2004; 22(17):3475–84. [PubMed: 15337795]
25. Morris EJ, Forman D, Thomas JD, et al. Surgical management and outcomes of colorectal cancer liver metastases. Br J Surg. 2010; 97(7):1110–8. [PubMed: 20632280]
26. Ksienski D, Woods R, Speers C, et al. Patterns of referral and resection among patients with liver-only metastatic colorectal cancer (MCRC). Ann Surg Oncol. 2010; 17(12):3085–93. [PubMed: 20839067]
27. Zieren HU, Müller JM, Zieren J, et al. The impact of patient's age on surgical therapy of colorectal liver metastases. Int Surg. 1993; 78(4):288–91. [PubMed: 8175253]
28. Zieren HU, Müller JM, Zieren J. Resection of colorectal liver metastases in old patients. Hepatogastroenterology. 1994; 41(1):34–7. [PubMed: 8175111]

29. Mayo SC, Heckman JE, Shore AD, et al. Shifting trends in liver-directed management of patients with colorectal liver metastasis: a population-based analysis. Surgery. 2011; 150(2):204–16. [PubMed: 21801959]
30. Monfardini L, Della Vigna P, Bonomo G, et al. Interventional oncology in the elderly: complications and early response in liver and kidney malignancies. J Geriatr Oncol. 2013; 4(1): 58–63. [PubMed: 24071493]
31. Sun E, Lakdawalla D, Reyes C, et al. The determinants of recent gains in cancer survival: An analysis of the Surveillance, Epidemiology, and End Results (SEER) database. ASCO. 2008; 26
32. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009; 27(22):3677–83. [PubMed: 19470929]
33. Howard DH, Kauh J, Lipscomb J. The value of new chemotherapeutic agents for metastatic colorectal cancer. Arch Intern Med. 2010; 170(6):537–42. [PubMed: 20233802]
34. Gallagher DJ, Kemeny N. Metastatic colorectal cancer: from improved survival to potential cure. Oncology. 2010; 78(3–4):237–48. [PubMed: 20523084]
35. Renehan AG, Egger M, Saunders MP, et al. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. BMJ. 2002; 324(7341):813. [PubMed: 11934773]
36. Jeffery GM, Hickey BE, Hider P. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev. 2002; (1):CD002200. [PubMed: 11869629]
37. Figueredo A, Rumble RB, Maroun J, et al. Follow-up of patients with curatively resected colorectal cancer: a practice guideline. BMC Cancer. 2003; 3:26. [PubMed: 14529575]
38. Mala T, Bøhler G, Mathisen Ø, et al. Hepatic resection for colorectal metastases: can preoperative scoring predict patient outcome? World J Surg. 2002; 26(11):1348–53. [PubMed: 12297926]
39. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999; 230(3):309–18. discussion 318–21. [PubMed: 10493478]
40. Ivanecz A, Potrc S, Horvat M, et al. The validity of clinical risk score for patients undergoing liver resection for colorectal metastases. Hepatogastroenterology. 2009; 56(94–95):1452–8. [PubMed: 19950809]
41. Mann CD, Metcalfe MS, Leopardi LN, et al. The clinical risk score: emerging as a reliable preoperative prognostic index in hepatectomy for colorectal metastases. Arch Surg. 2004; 139(11): 1168–72. [PubMed: 15545561]

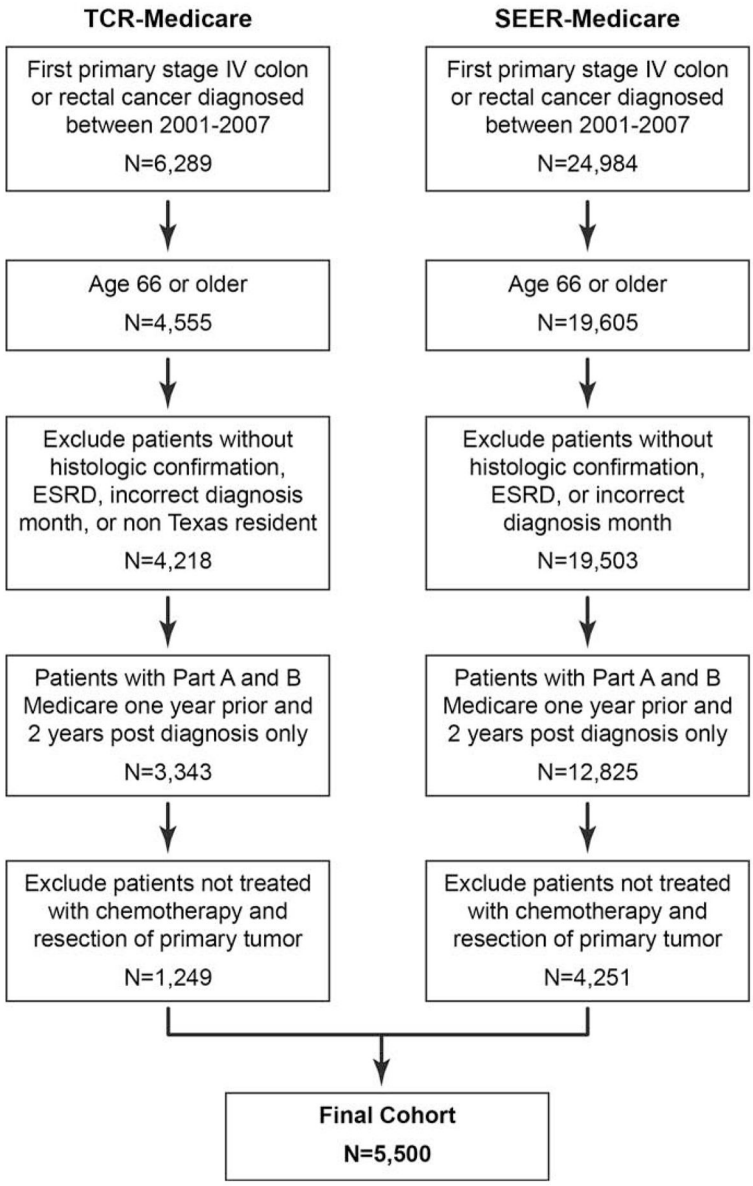

Figure 1.

Cohort selection. TCR- and SEER-Medicare linked data for patients presenting with stage IV colorectal cancer. Patients who did not have Medicare Parts A and B coverage without HMO for one-year prior and two years following diagnosis were excluded. Only patients undergoing resection of the primary tumor and chemotherapy were included. The final cohort included 5,500 patients.

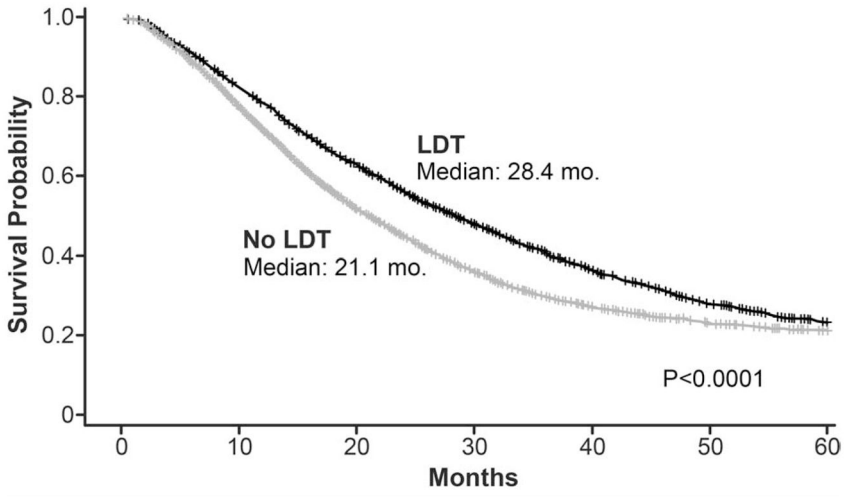

Figure 2.

Time trends in use of liver directed therapy. Rates of liver directed therapy remained stable over time (34.1% in 2001 vs. 33.4% in 2007, P=NS).

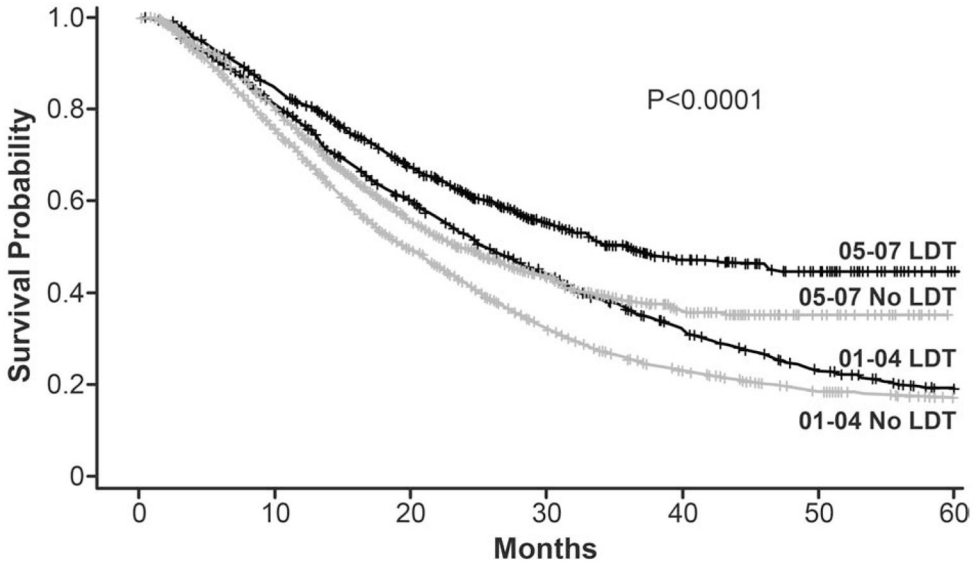

Figure 3.

Timing of liver directed therapy in relation to treatment of the primary tumor in patients undergoing treatment of liver metastases. A) Timing of liver directed therapy relative to resection of the primary tumor. 74.4% of patients underwent liver directed therapy at the time of primary tumor resection. B) Timing of chemotherapy relative to resection of the primary tumor and liver directed therapy. 76.0% of patients received chemotherapy as the initial treatment modality. 16.6% of patients received chemotherapy between resection of the primary tumor and liver directed therapy.

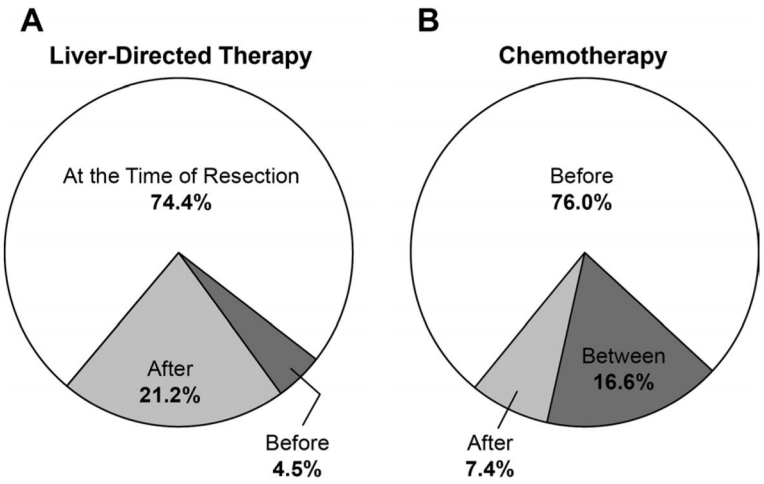

Figure 4.

Kaplan-Meier analysis of the five-year disease specific survival for patients treated with resection of the primary tumor and chemotherapy stratified by receipt of liver directed therapy. Median survival was 28.4 months for patients undergoing liver-directed therapy compared to 21.1 months in patients who did not receive treatment for liver metastases ($P<0.0001$).

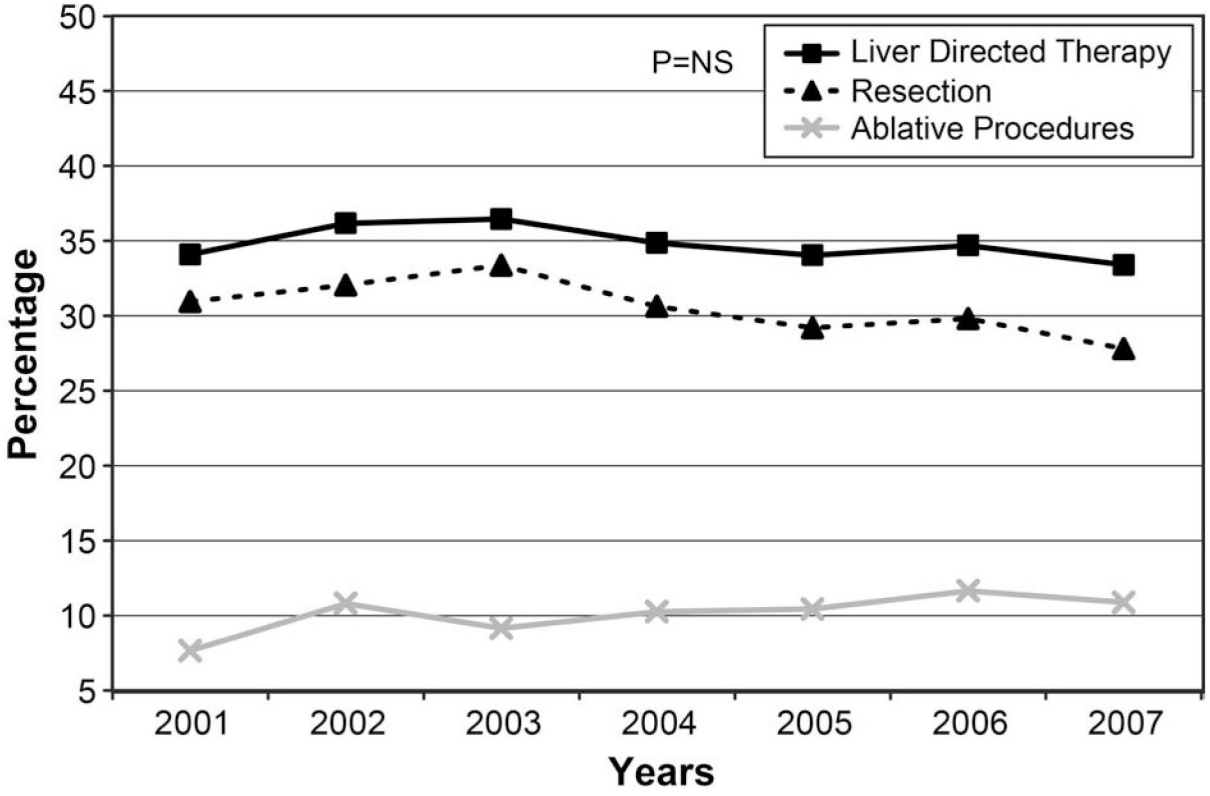

Figure 5.

Kaplan-Meier analysis of the five-year disease specific survival for patients treated with resection of the primary tumor and chemotherapy ± liver directed therapy, stratified by early and late time periods. Median survival improved over time, from 25.4 months to 35.9 months in patients undergoing liver directed therapy (P<0.0001). Median survival also improved for patients who did not receive liver directed therapy (19.6 months vs. 23.4 months, P<0.0001).

Table 1

ICD-9 diagnosis codes used to identify colorectal cancer, treatment, and sites of metastatic disease in patients presenting with stage IV colorectal cancer

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: v58.1, v66.2, and v67.2 HCPCS and CPT codes: Q0083-Q0085, 51720, J0640, 964XX, 96400–96549, J9000-J9999, G0355-G0363, G9021- G9032
Modern chemotherapy (oxaliplatin, irinotecan, or bevacizumab containing regimens)	J9263, J9206, and J9035
Standard chemotherapy (5FU/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

J Surg Res. Author manuscript; available in PMC 2015 September 01.

Table 2

Summary of overall cohort and bivariate analysis of factors associated with receipt of any liver directed therapy and liver resection in older adults with stage IV colorectal cancer

Factor (p-value)	Overall cohort N=5,500 (% of overall cohort)	Liver directed therapy N=1,918 (% Receiving LDT)	Liver resection N= 1,686 (% Receiving liver resection)
Gender			
Female	2,758 (50.2%)	909 (33.0%)	797 (28.9%)
Age (mean) *§	74.3 ± 5.7	73.8 ± 5.5	73.7 ± 5.5
66–69 yrs	1,339 (24.4%)	516 (38.5%)	452 (33.8%)
70–74 yrs	1,653 (30.1%)	611 (37.0%)	547 (33.1%)
75–79 yrs	1,430 (26.0%)	489 (34.2%)	425 (29.7%)
80–84 yrs	789 (14.3%)	229 (29.0%)	202 (25.6%)
85+ yrs	289 (5.2%)	73 (25.3%)	60 (20.8%)
Race			
White	4,666 (84.9%)	1,648 (35.3%)	1,449 (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	3,522 (64.0%)	1,220 (34.6%)	1,071 (30.4%)
1	1,309 (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	4,532 (82.4%)	1,561 (34.4%)	1,386 (30.6%)
Rectum	968 (17.6%)	357 (36.9%)	300 (31.0%)
Poorly differentiated tumors	1,611 (29.3%)	488 (30.3%)	433 (26.9%)
Emergency surgery			
Yes	1,109 (20.2%)	368 (33.2%)	335 (30.2%)
No	4,391 (79.8%)	1,550 (35.3%)	1,351 (30.8%)
Chemotherapy *§			

Factor (p-value)	Overall cohort N=5,500 (% of overall cohort)	Liver directed therapy N=1,918 (% Receiving LDT)	Liver resection N= 1,686 (% Receiving liver resection)
Standard	1,599 (29.1%)	478 (29.9%)	427 (26.7%)
Modern	3,123 (56.8%)	1,197 (38.3%)	1,050 (33.6%)
Other	778 (14.2%)	243 (31.2%)	209 (26.9%)
Bevacizumab *§			
Yes	1,535 (27.9%)	602 (39.2%)	514 (33.5%)
Liver directed therapy			
Resection	1,686 (30.7%)	NA	NA
Ablation/embolization	554 (10.1%)	NA	NA
Time period§			
2001–2004	3,313 (60.2%)	1,173 (35.4%)	1,052 (31.8%)
2005–2007	2,187 (39.8%)	745 (34.1%)	634 (29.0%)

* denotes P<0.0001 for liver directed therapy

§ denotes P≤0.030 for liver resection

P values for χ^2 analysis representing any difference within categories

Table 3

Multivariate analysis of factors associated with liver directed therapy in patients with stage IV colorectal cancer

Factor (REF)	Odds Ratio	Confidence Interval
Year of diagnosis	0.96	0.93–0.99
Age (66–69 yrs)		
70–74 yrs	0.94	0.81–1.10
75–79 yrs	0.87	0.74–1.02
80–84 yrs	0.71	0.89–0.87
≥ 85 yrs	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)		

Factor (REF)	Odds Ratio	Confidence Interval
Modern	1.44	1.25–1.66
Other	1.11	0.92–1.35

Table 4

Cox models for five-year disease specific survival for the overall cohort, in the early time period (2001–2004) and late time 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)
Time period (2001–2004)	0.68 (0.63–0.73)	NA	NA
Age (66–69 yrs)			
70–74 yrs	1.13 (1.03–1.24)	1.09 (0.97–1.22)	1.20 (1.02–1.41)
75–79 yrs	1.23 (1.12–1.36)	1.20 (1.07–1.35)	1.28 (1.08–1.52)
80–84 yrs	1.40 (1.25–1.56)	1.37 (1.20–1.57)	1.46 (1.21–1.78)
≥ 85 yrs	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)

Interaction between time period and receipt of liver directed therapy P=0.04