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Trends and Comparative Effectiveness in Treatment of Stage IV Colorectal Adenocarcinoma

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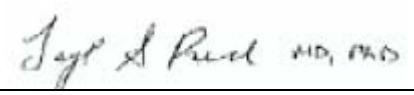

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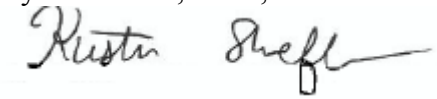

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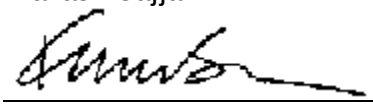

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Trends and Comparative Effectiveness in Treatment of Stage IV Colorectal Adenocarcinoma

by

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Thesis

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TRENDS AND COMPARATIVE EFFECTIVENESS IN TREATMENT OF STAGE IV COLORECTAL ADENOCARCINOMA

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Abstract: The management of patients with stage IV colorectal cancer is evolving. Primary treatment modalities include systemic chemotherapy, resection of the primary tumor, and, in select cases, resection of metastatic disease. Historically, stage IV disease was first managed with surgical resection to prevent complications such as obstruction, bleeding, and perforation prior to starting chemotherapy. The improved efficacy of newer oxaliplatin- and irinotecan-based chemotherapeutic regimens combined with the low incidence of tumor related complications has led surgeons and oncologists to question the utility and, when indicated, the timing of elective resection of the primary tumor in asymptomatic patients with metastatic disease. In addition, the indications for liver resection and liver ablative techniques for metastatic disease have increased.

In older patients, the morbidity and mortality following colon resection is significant. The role and timing of surgical resection relative to chemotherapy as well as aggressive management of liver metastases is even more controversial in this vulnerable population. Our first goal was to use Texas Cancer Registry (TCR) and Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data to evaluate the current management in older patients presenting with stage IV colorectal cancer, including receipt of chemotherapy, type of chemotherapy, resection of the primary tumor, and the management of liver metastases in a population-based, observational cohort. Next, in patients undergoing chemotherapy and/or elective resection of the primary tumor, we examined trends in the timing of chemotherapy and resection of the primary tumor and evaluated the comparative effectiveness when chemotherapy versus resection of the primary tumor was used as the initial treatment modality. Finally, we evaluated trends and outcomes in liver-directed therapy for metastatic disease in this population.

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Chapter 1: Trends in Treatment and Survival in Older Patients Presenting with Stage IV Colorectal Cancer

INTRODUCTION

Twenty percent of patients with colorectal cancer present with metastatic (stage IV) disease at the time of diagnosis.[1] For stage IV disease, treatment with curative intent is only possible in the small subset of patients presenting with limited metastatic disease burden. While long-term survival has been reported after aggressive treatment in highly selected patients with limited synchronous or metachronous metastatic disease, the overall 5-year survival in patients presenting with stage IV disease is only 6%.[2]

Prior to the year 2000, 5-fluorouracil (5-FU)/leucovorin (LV) was the standard chemotherapeutic regimen for patients with stage IV disease. In 2000, phase III studies and randomized clinical trials demonstrated a survival benefit in patients receiving oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) combined with 5-FU/LV when compared to 5-FU/LV alone.[3-5] Consequently, FOLFOX and FOLFIRI became first line chemotherapy for advanced colorectal cancer. Several other agents have subsequently been approved for treatment in combination with FOLFOX or FOLFIRI. These include capecitabine, bevacizumab, and cetuximab.[6-10]

Historically, patients with stage IV colorectal cancer underwent resection of the primary tumor to minimize tumor related complications such as obstruction, bleeding, or perforation. A previous study using SEER-Medicare data from 1991-1999 demonstrated a 72% cancer directed surgery rate in older patients.[11] The mortality of cancer-directed surgery in older patients has been reported to range from 10% to18%.[11, 12] Given the advances in chemotherapy and palliative techniques such as endoluminal stenting since this study, and the high mortality of cancer-directed surgery, the role of elective resection in stage IV disease has become controversial.[10-13]

Our initial goal was to evaluate trends in the management and outcomes of older patients presenting with stage IV colorectal cancer since the introduction of modern chemotherapeutic agents. First, we evaluated the adoption of newer cytotoxic regimens including oxaliplatin, irinotecan, and bevacizumab. Second, we described the trends in use of surgical resection of the primary tumor since the previous report and after the introduction of more efficacious systemic therapy. Finally, to assess the influence of these practice changes on survival we evaluated disease-specific survival over this same time period.

METHODS

The Institutional Review Board at the University of Texas Medical Branch determined this study to be exempt from review. The Texas Department of State Health Services approved the study, as did the privacy review board of the Centers for Medicare and Medicaid Services. Data use agreements have been signed with both data providers.

Data Source

Data from the Texas Cancer Registry (TCR) and Surveillance Epidemiology and End Results (SEER)-Medicare linked database were used for the analysis. The TCR data set provides detailed information about elderly adults with cancer in Texas. SEER collects data on cancer cases from population-based cancer registries covering approximately 28% of the US population. Both registries collect data on patient demographics, primary tumor site, stage, first course of treatment, tumor morphology, cause of death, and survival.[14, 15] Through the National Cancer Institute (NCI) and Center for Medicare and Medicaid Services (CMS), approximately 98% of all people aged 65 and older in TCR and 93% in SEER are matched with Medicare enrollment and claims files.[16, 17] The Medicare claims data include information on hospital stays, physician services, and hospital outpatient visits.[18] The Medicare files used for this study included the 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).[18]

Study Sample and Outcome Measures

The cohort selection is shown in Figure 1. The final sample included 16,168 patients (Figure 1, pg 55). We included cancer patients diagnosed with stage IV colorectal cancer between 2001 and 2007 and their Medicare claims from 2000 through 2009. This allowed us to determine patient comorbidity in the year prior to diagnosis and to follow all patients for two years or until death.

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 and *Current Procedural Terminology, Fourth Edition* (CPT-4) codes for colorectal resection (Table 1). These codes included colon and rectal resections, both open and laparoscopic, with or without colostomy. Patients who underwent stoma formation without resection or stent placement were not classified as having resection of the primary tumor. Emergent resection was defined as follows: a colorectal resection classified as "emergent" in the MEDPAR file, or any colorectal resection performed prior to or subsequent to systemic treatment with chemotherapy with a diagnosis code for obstruction, bleeding, or perforation (or related diagnosis) (Table 1).

Chemotherapy was identified using Healthcare Common Procedure Coding System (HCPCS) Codes, ICD-9 procedure and diagnosis codes, J codes, and revenue center codes for administration of chemotherapy as defined by SEER-Medicare.[19] A beneficiary was considered to have received chemotherapy if he/she had a claim for chemotherapy after the diagnosis of colorectal cancer (Table 1). Specific agents were identified using J codes (Table 1). We defined "standard" chemotherapy as 5-fluorouracil $\pm$ leucovorin and "modern" chemotherapy as any regimen containing oxaliplatin or irinotecan. We were unable to assess the use of capecitabine, an oral analog of 5-fluorouracil, as orally administered agents cannot be identified in the Medicare parts A and B claims data. If a claim for leucovorin without 5-fluorouracil, oxaliplatin, or irinotecan was found, the patient was assumed to have received standard chemotherapy, as it is possible they may have been treated with capecitabine. Regimens not meeting

these definitions were classified as "other". Standard or modern chemotherapy regimens as defined above were given in 84.3% of patients identified as having received chemotherapy.

Covariates

Patient characteristics included age, sex, race, Charlson comorbidity index (0, 1, 2, and 3 or more), and year of diagnosis. Median income and percent of residents with <12 years education were determined at the zip code level. Based on these variables, quartiles of education and income were established with quartile one being the lowest education/income and quartile four, the highest. Tumor characteristics included type (colon vs. rectum), site (right, left, transverse, rectum, and unspecified), nodal status (negative, positive, no nodes, or unknown), and tumor differentiation (well/moderately vs. poorly vs. other). Rectal cancer was defined by site code for rectal cancer (26) or site code for rectosigmoid cancer (25) plus a rectal cancer operation (low anterior resection or abdominoperineal resection) and/or radiation.

Analysis

We calculated summary statistics for the overall cohort and determined the percentage of patients undergoing each treatment modality. The number of patients undergoing resection of the primary tumor was determined. For patients who received chemotherapy, we determined the percentage receiving standard chemotherapy and modern chemotherapy. Bevacizumab received FDA approval for use in advanced colorectal cancer in 2004. For this analysis, its use was evaluated independently of other chemotherapeutic regimens.

We used a Cochran-Armitage test for trends to evaluate the trends in resection of the primary tumor, use of chemotherapy, and chemotherapy type. A logistic regression model was used to evaluate the independent association between year of diagnosis and resection of the primary tumor. In this model, year was defined as a continuous variable with the odds ratio representing the increase or decrease per year of diagnosis. Unadjusted disease specific survival was evaluated using a Kaplan-Meier analysis. A Cox proportional hazards model was used to evaluate improvements in five-year disease specific survival over time.

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 16,168 beneficiaries with stage IV colon cancer on presentation who met the inclusion criteria (Figure 1). The mean age of the study population was 77.8 ± 7.3 years. Females comprised 53.8% of the cohort. The majority of patients were white (82.9%) and had a Charlson comorbidity score of zero (57.7%). The colon was the primary site of cancer in 83.4% of patients and the rectum in 16.6% of patients. Further breakdown of the distribution of cancers throughout the colon is listed in Table 2.

Treatment

The characteristics of the treated and untreated patients are shown in Table 2. Resection alone was performed in 27.4% of patients, chemotherapy alone was administered to 11.1% of patients, and 27.5% of patients did not receive treatment.

Thirty-four percent of patients (N=5,500) received chemotherapy and underwent resection of the primary tumor. In patients undergoing both treatment modalities, resection was performed prior to chemotherapy in 91.2% of patients.

Resection of the primary tumor with or without chemotherapy was performed in 9,935 patients (61.5%). Resection was emergent in 26.8% of the 9,935 patients. The 30-day operative mortality was 10.2% for patients undergoing elective resection and 21.5% for patients undergoing emergent resection.

Systemic chemotherapy was administered to 7,292 patients (45.1%). Of the 7,292 patients, 4,081 (56.0%) were treated with modern regimens containing oxaliplatin or irinotecan, 2,069 (28.4%) were treated with the standard regimen, and 1,142 (15.7%) were treated with other regimens. The most common agents identified in those receiving other chemotherapeutic regimens included: carboplatin, cisplatin, gemcitabine, cetuximab, and docetaxel.

Bevacizumab was given to 27.4% of patients treated with systemic chemotherapy. Bevacizumab was administered in combination with a modern chemotherapy regimen in 83.1% of patients, with a standard chemotherapy regimen in 11.8%, and another regimen in 5.1% of patients.

Liver resection was performed in 17.6% of patients (N=2,846). Ablation was performed in 3.2% (N=515) and chemoembolization in 1.2% of patients (N=193).

Time Trends in Treatment

Resection rates decreased from 64.6% in 2001 to 57.1% in 2007 ($P<0.0001$). The rate of elective resection decreased from 49.5% in 2001 to 40.9% in 2007 ($P<0.0001$, Figure 2A, pg 56).

The overall administration of chemotherapy remained stable over the study period (P=0.48); however, among patients who received any chemotherapy, the use of oxaliplatin or irinotecan containing regimens increased from 40.9% in 2001 to 75.4% in 2007 (P<0.0001) (Figure 2B, pg 56). Use of bevacizumab increased over time, with the greatest rate of increased use noted in 2003 shortly before it received FDA approval for use in advanced colorectal cancers (Figure 2C, pg 56).

The percent of patients who underwent both resection and chemotherapy remained stable, with approximately 30-35% of the cohort receiving both treatments across time (Figure 2D). The use of chemotherapy as the only treatment modality increased over time from 9.8% to 13.9% from 2001-2007 (P<0.0001) while at the same time, the proportion of patients undergoing resection alone decreased (29.8% to 26.0%, P<0.0001, Figure 2D, pg 56).

Factors Associated with Resection of the Primary Tumor (Table 3)

After controlling for demographics and receipt of chemotherapy, the year of diagnosis remained a significant predictor of resection of the primary tumor, with a 3% decrease in resection with each increasing year of diagnosis (OR 0.97; 95% CI 0.95-0.99). Younger patients and those with poorly differentiated colonic primaries had an increased likelihood of undergoing resection of the primary tumor.

Survival

The two-year and five-year disease-specific survival rates for the entire cohort were 27.4% and 12.9% respectively. In an unadjusted analysis, survival improved over time with a 25.2% two-year disease specific survival in the early time period (2001-2004) compared to a 30.7% two-year disease specific survival in the later time period, (2005-

2007, P<0.0001). In the Cox proportional hazards model for the overall cohort (Table 4), for each one-year increase in the diagnosis year, the hazard of death decreased by an estimated 4% (HR 0.96; 95% CI 0.95-0.97). Resection of the primary tumor (emergent or elective), receipt of chemotherapy, and receipt of bevacizumab were independently associated with improved survival. Advancing age at diagnosis, colon cancers, and poorly differentiated tumors were associated with worse prognosis.

DISCUSSION

This study is the first to evaluate treatment patterns and outcomes in older colorectal cancer patients presenting with stage IV disease in the era of modern chemotherapy. Time trends demonstrate an increase in the use of oxaliplatin and irinotecan containing regimens after studies in 2000 demonstrated their efficacy and superiority in improving survival when compared to the standard 5-FU and leucovorin regimen.[3-5] Similarly, the use of bevacizumab has increased since it received FDA approval for use in stage IV colorectal cancer in 2004.

Through 2007, surgical resection was performed in the majority of patients presenting with advanced disease and was the first treatment modality in most patients receiving combination surgical resection and chemotherapy. However, we observed a statistically significant decrease in the rate of surgical resection of the primary tumor from 64.6% in 2001 to 57.1% in 2007. This decrease is even more dramatic when compared to the 72% rate of resection of the primary tumor reported in a study using SEER-Medicare linked data from 1991 to 1999.[11] A 2010 study of 103,744 patients from the Netherlands Cancer Registry also demonstrated a decline in primary tumor resection

rates from 66% to 56% (P<0.001) and a dramatic rise in chemotherapy use from 2% in 1989-1993 to 40% in 2004-2006 (P<0.001) in older patients with stage IV disease.[20]

In addition to the treatment trends, we observed an improvement in survival over time, consistent with other studies using tumor registry data.[21, 22] As in our study, the Netherlands Cancer Registry study found an independent association between year of diagnosis and survival.[20] The improved survival over time in our study was not entirely mediated by treatment, as year of diagnosis remained significantly associated with survival even after adjusting for chemotherapy, resection of the primary tumor, and metastasectomy. Taken together, the decreased resection rates, increased use of modern chemotherapeutic agents, and the improved survival over time suggest better allocation of patients to appropriate treatment groups. These data suggest that we are aggressively treating the patients who will benefit most and avoiding unnecessary operations or aggressive therapy in those who are not likely to benefit. Additional factors that may explain improvements in survival above those attributed to treatment include advances in surgical technique, improvements in prevention, recognition, and management of complications, improved imaging leading to more accurate staging and diagnosis of treatable metastases and subsequently, more appropriate treatment allocation.

Our analysis shows that the number of patients receiving chemotherapy alone increased. This increase in chemotherapy alone may represent the beginning of a paradigm shift in the treatment of stage IV disease, allowing us to reserve elective resection of the primary tumor for patients with limited disease burden or those who exhibit a good response to chemotherapy. Continued evaluation of these trends as more data are available will confirm changes based on the current National Comprehensive

Cancer Network (NCCN) recommendations, where immediate colon resection is reserved for patients at imminent risk for obstruction or significant bleeding.[23]

Our study has several limitations. We evaluated the management of stage IV disease in older patients; therefore, the results may not be generalizable to younger patients presenting with advanced colorectal cancer. However, older patients are often not included in randomized controlled trials and have a high-risk of treatment related morbidity and mortality. As such, it is important to study the comparative effectiveness of different treatment strategies in this vulnerable population. We were unable to evaluate the use of newer chemotherapeutic agents, such as panitumumab and aflibercept, which were introduced after the study period. In addition, we could not capture the use of capecitabine, using SEER-Medicare data from 2001-2007, as this is administered orally. If a patient was only treated with leucovorin, we placed them in the standard chemotherapy group because it is possible they were treated with capecitabine; this occurred in only 0.4% of patients receiving chemotherapy. These data do not allow us to evaluate the intent of treatment. For example, we cannot determine which patients received chemotherapy with the intent to undergo resection in the future versus those who received chemotherapy purely with palliative intent. Similarly, we are unable to determine which resections were performed to palliate symptoms and which were performed in asymptomatic patients, but we were able to identify emergent vs. elective resections. Lastly, there is selection bias; aggressive treatment is more likely to be pursued in healthier patients and patients with lower burden of disease. The observed improved survival over time partly reflects proper patient selection for surgical resection and aggressive therapy.

Our study demonstrates that practitioners are rapidly adopting the use of newer chemotherapeutic agents and employing elective surgical resection less often. These changes are associated with improved survival over time. Colorectal cancer is primarily a disease of the elderly, yet older patients account for only 40% of patients included in clinical trials.[24] While there is no question as to the role of surgical resection in symptomatic patients, the high operative mortality associated with elective resection in older patients presenting with stage IV disease makes elective resection controversial in the setting of modern chemotherapy. Further studies are needed to determine if we are, in fact, observing a paradigm shift. As more data becomes available, we can evaluate adherence to the current NCCN treatment guidelines and evaluate the comparative effectiveness of a chemotherapy first approach in this vulnerable population of patients.

Chapter 2: Timing of Chemotherapy and Primary Tumor Resection in Older Patients Presenting with Stage IV Colorectal Cancer

INTRODUCTION

This study expands on the previous chapter. It describes adherence to the current NCCN treatment guidelines and evaluates the comparative effectiveness of chemotherapy versus resection of the primary tumor as the initial treatment modality in older patients presenting with stage IV colorectal cancer. The optimal timing of chemotherapy and resection of the primary tumor is controversial for patients presenting with stage IV colorectal cancer. Timing of therapy is especially controversial in older patients where the morbidity and mortality associated with colorectal resection is high.

Historically, stage IV disease was first managed with surgical resection to prevent complications such as obstruction, bleeding, and perforation prior to starting chemotherapy. However, the reported incidence of tumor related complications is low.[25] In addition, oxaliplatin and irinotecan based chemotherapeutic regimens have demonstrated improved efficacy and are associated with significant response of the primary tumor compared with the traditional treatment of 5-FU/leucovorin alone.[3-5] This has led surgeons and oncologists to question the utility and, when indicated, the timing of elective resection of the primary tumor in asymptomatic patients with metastatic disease.[25, 26]

The purpose of our study was to evaluate population-based trends in use of chemotherapy as the first treatment modality since the introduction of oxaliplatin and

irinotecan containing regimens and to evaluate the association between the timing of chemotherapy and surgical resection and survival.

METHODS

The Institutional Review Board at the University of Texas Medical Branch determined this study to be exempt from review. The Texas Department of State Health Services approved the study, as did the privacy review board of the Centers for Medicare and Medicaid Services. Data use agreements have been signed with both data providers.

Data Source

As previously described, data from the Texas Cancer Registry (TCR) and Surveillance Epidemiology and End Results (SEER)-Medicare linked database (2000-2009) were used for the analysis.

Study Sample and Outcome Measures

Our cohort selection is diagrammed in Figure 3 (pg 57). We identified 31,273 patients with stage IV colorectal cancer diagnosed between 2001 and 2007. Medicare claims from 2000 through 2009 were used to determine comorbidities one year prior to diagnosis and to allow for follow up of all patients for two years or until death.

We excluded patients with Medicare benefits due to end-stage renal disease, patients without histologic confirmation of adenocarcinoma of the colon or rectum, and those diagnosed at autopsy or on death certificate only. Our cohort was limited to patients who underwent treatment for stage IV disease, defined as elective surgical resection of the primary tumor, systemic chemotherapy, or both. We excluded patients who did not have Medicare Parts A and B and those with HMO coverage in the one year before and two years following diagnosis. Finally, we excluded patients undergoing

emergent resection. Emergent resection was defined as a colorectal resection coded as "emergent" in the MEDPAR file or a colorectal resection associated with a primary diagnosis code for obstruction, bleeding, or perforation (or related diagnosis) (Table 1). The study sample included 7,738 beneficiaries.

Resection of the primary tumor, receipt of chemotherapy, and specific chemotherapeutic regimens were defined as described in chapter 1.

Covariates

Covariates were described in Chapter 1 (Table 1). This study also evaluated the use of metastasectomy, which was defined as liver or pulmonary resection following a colon or rectal cancer diagnosis (CPT and ICD-9 codes also listed in Table 1).

Analysis

Summary statistics were calculated for the overall cohort and the percentage of patients undergoing each treatment modality was determined. Patients were classified into treatment groups based on the initial treatment modality received and labeled "chemotherapy" and "resection" groups (Figure 4, pg 58), regardless of subsequent treatment with the alternate modality. For example, if a patient underwent resection of the primary tumor followed by chemotherapy, or resection without subsequent chemotherapy, he/she was analyzed in the resection group.

We used a Cochran-Armitage test for trend to evaluate time trends in receipt of chemotherapy as the first treatment modality. Kaplan-Meier survival analysis was performed to determine unadjusted three-year disease specific survival for both treatment groups. A Cox proportional hazards model was used to determine the independent association between the initial treatment modality and survival. This analysis included

initial treatment modality, year of diagnosis, age, sex, race, Charlson comorbidity index score, cancer type, and metastasectomy.

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

We identified 7,738 beneficiaries who met our inclusion criteria. The patient, treatment, and tumor characteristics of the cohort are summarized in Table 5. The average age of the cohort was 77.7 ± 7.2 years. Females comprised 53.8% of the cohort. Most patients were white (83.9%) and had a Charlson comorbidity score of zero (57.9%). Colon primaries comprised 81.4% of tumors and 27.8% were poorly differentiated. Chemotherapy was administered to 42.7% of patients, with the majority receiving oxaliplatin or irinotecan based regimens. Resection of the primary tumor was performed in 76.8% of patients and metastasectomy (lung or liver resection) was performed in 20.2% of patients. The 30-day operative mortality for patients undergoing surgical resection of the primary tumor was 23.0%.

The first treatment modality was chemotherapy in 29.4% and resection of the primary tumor in 70.6% of patients (Table 5; Figure 4, pg 58). Of the patients receiving chemotherapy as the first treatment modality, 78.7% (N=1,792) did not undergo resection of the primary tumor. Of those undergoing resection of the primary tumor as the first treatment modality, 81.2% (N=4,435) did not receive systemic therapy (Figure 4, pg 58). The use of chemotherapy as the first treatment modality increased from 25.2% in 2001 to 35.2% in 2007 (Figure 5, pg 59; $p<.0001$). For the subset of patient with rectal cancer,

rates of chemotherapy as the initial treatment modality were higher compared to those with colon cancer (57.3% vs. 23.0%; p<.0001). In this subset, the use of chemotherapy as first treatment over time increased from 49.0% in 2001 to 66.9% in 2007 (p<.0001). For colon cancer patients the use of chemotherapy first increased from 20.4% in 2001 to 28.2% in 2007 (p<.0001).

Bivariate analyses comparing patient and tumor characteristics between the two treatment groups are shown in Table 6. Patients in the resection group were older, had increased Charlson comorbidity scores, and were more likely to have colon vs. rectal cancers. Metastasectomy was more commonly performed in patients in the resection group.

For the overall cohort, the unadjusted median 3-year disease specific survival for patients in the chemotherapy group was 13.1 months compared to 7.2 months in the resection group (Figure 6A, pg 60; p<.0001). In patients who were treated with both chemotherapy and surgical resection of the primary tumor, the median survival for patients receiving chemotherapy first was 26.4 months compared to 25.5 months in patients undergoing resection first (p=NS; Figure 6B, pg 60), with similar disease-specific 3-year survival.

In a Cox proportional hazards model controlling for age, sex, race, Charlson comorbidity score, tumor type, and metastasectomy, chemotherapy as the initial treatment modality was associated with improved 3-year survival (HR 0.90, 95% CI 0.84-0.95). Increasing year of diagnosis was also associated with improved survival (HR 0.95, 95% CI 0.94-0.96). Additional factors associated with worse prognosis were advancing age, a Charlson comorbidity score ≥ 3, and colon cancers (Table 7).

DISCUSSION

In patients presenting with metastatic colorectal cancer, surgical resection of the primary tumor has been the preferred initial treatment approach. However, in 2006 the National Comprehensive Cancer Network began advocating chemotherapy as the initial treatment modality for asymptomatic patients with unresectable synchronous metastases, based on the panel's review of available evidence. Since then, the recommendations have continued to support initial treatment with chemotherapy for these patients.[23, 27] While our data show an increase in the use of chemotherapy as the initial treatment modality over time, only 66.9% of older patients with rectal cancer and 28.2% of patients with colon cancer received chemotherapy as the initial treatment modality by 2007.

Our data demonstrate that chemotherapy as the initial treatment modality is associated with improved survival after controlling for patient, tumor, and treatment factors. This treatment approach offers several advantages: 1) ability to assess the tumor's response to treatment, 2) delivery of chemotherapy to a tumor with intact blood supply, and 3) avoidance of surgical morbidity in patients with early disease progression. It is important to note that we cannot determine the intended initial treatment plan from the claims data. We attempted to eliminate patients requiring emergent resection, leaving patients that could have received either chemotherapy or resection as the initial treatment modality. We made the assumption that patients undergoing resection of the primary tumor as the initial treatment modality did so with the intent to receive systemic chemotherapy and, conversely, patients initially treated with chemotherapy did so with the intent of undergoing resection if tumor response was good. In clinical practice, surgical resection is most often offered with the intent to administer chemotherapy in the

future; however, it is possible that some patients required resection for palliation of symptoms despite our efforts to eliminate emergent resection. Similarly, given the low rate of resection following chemotherapy, it is likely that chemotherapy may have been administered with pure palliative intent in some patients. In this time period where resection was the more common initial treatment modality, we hypothesize that patients receiving chemotherapy as the initial treatment modality had more extensive disease, unfavorable primary tumor characteristics, or poorer performance status.

Our findings support conclusions from a systematic review and meta-analysis of studies comparing outcomes with initial resection of the primary tumor versus initial treatment with systemic therapy in patients with stage IV disease. [28] In patients treated with chemotherapy first, the rate of obstruction was 13.9%. This was similar to the rate of major complications in patients treated with initial resection of the primary tumor. Major postoperative complications including hemorrhage, sepsis, or anastomotic leak occurred in 11.8% and minor complications, such as surgical site infections and urinary tract infections, occurred in 20.6% of patients. The authors concluded that for patients with unresectable metastatic colorectal cancer, resection of the primary tumor in asymptomatic patients provides minimal benefit.[28] These data led the authors to suggest that a chemotherapy first approach may be a safe and reasonable option.

Our study demonstrates a 23% operative mortality in older patients undergoing colorectal resection for stage IV disease, consistent with previous studies demonstrating poor short-term outcomes in older patients undergoing major abdominal operations.[29-31] A large systematic review evaluating outcomes following colorectal cancer surgery in patients < 65 and ≥ 65 years of age found an association between advancing age and

increased postoperative morbidity and mortality and a reduction in overall survival for elderly patients.[32] Similarly, the total number of days in the hospital in the first year after surgery for colorectal cancer increases with increasing age.[33]

Conversely, the ability of older patients to tolerate treatment of colorectal cancer with fluorouracil based chemotherapy regimens has been demonstrated.[34, 35] Pooled age-based analysis from four randomized clinical trials administering oxaliplatin plus fluorouracil/leucovorin (FOLFOX4) and irinotecan plus fluorouracil/leucovorin in colorectal cancer patients demonstrated no difference in efficacy and toxicity between patients younger than 70 and those 70 years or older.[36, 37]

The largest limitation of our study is selection bias. There may be patients in this cohort who were treated with either chemotherapy or surgery for palliative purposes. It could be argued that a direct comparison between the two groups is not appropriate as it is possible that important unmeasurable differences are present and the survival benefit demonstrated by our study is influenced by confounding. However, given the probable direction of the selection bias as discussed above, we would expect the chemotherapy group to have worse outcomes. Therefore, the observed improved disease-free survival with initial chemotherapy treatment is even more striking.

Our study further supports the use of chemotherapy as the initial treatment modality in older patients presenting with stage IV colorectal cancer and demonstrates significant underuse of chemotherapy as the initial treatment modality. Our results support prior studies suggesting that chemotherapy should be the initial approach, given the low incidence of complications from an intact primary tumor and the high postoperative mortality observed with colorectal cancer resections. At this time, a multi-

center, randomized, controlled trial is underway in Europe with the primary aim to determine the efficacy of initial primary tumor resection in patients with colon cancer and unresectable synchronous metastases.[38] Until the results of such prospective randomized studies become available, practitioners should reserve initial surgical resection of the primary tumor for symptomatic patients or those at high risk for tumor complications.

Chapter 3: Management of Synchronous Liver Metastases in Older Patients with Colorectal Cancer

INTRODUCTION

A comprehensive study of the management stage IV colorectal cancer necessitates evaluation of the management of metastatic disease. For patients with colorectal cancer, metastatic disease is present at the time of diagnosis in 20% of cases, and for these patients the liver is the most common site of metastatic disease.[39, 40] 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, local ablative techniques, and chemoembolization are the primary modalities available for treatment of hepatic metastases. In carefully selected patients with liver metastases, treatment with aggressive multimodality therapy has led to 5-year survival rates exceeding 50%.[41]

Liver resection is the only potentially curative option and the preferred treatment modality in patients with isolated and resectable liver metastases. 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 directed chemotherapy are alternative techniques to decrease tumor burden and prolong survival.[42] While single institution, retrospective studies from specialized centers have demonstrated low mortality rates in carefully selected older patients undergoing liver resection,[43-50]

there is a paucity of population-based data on the current management and outcomes of liver directed therapy in older patients with colorectal cancer.[43]

The goal of our study was to use population-based data to evaluate the current trends in the management of stage IV colorectal cancer (CRC) in older patients. We specifically evaluated the modalities used, the timing of liver directed therapy in relation to treatment of the primary tumor and receipt of systemic therapy, and time trends in the use of various modalities. Finally, we evaluated 30-day mortality and long-term survival for different modalities of liver directed therapy.

METHODS

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

Data Source

As previously described, we used Texas Cancer Registry- (TCR) and Surveillance Epidemiology and End Results- (SEER) linked Medicare data from 2000-2009.

Cohort Selection

We selected patients with a first stage IV primary colorectal adenocarcinoma diagnosed between 2001 and 2007 (ICD-O-3 histology codes, Table 1) with Medicare Parts A and B coverage without HMO for one-year prior and two years following diagnosis. We excluded patients who did not undergo resection of the primary tumor and did not receive chemotherapy. 5,500 patients met our inclusion criteria.

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

Treatment of the primary tumor and receipt of chemotherapy were defined as above. Medicare claims in inpatient, outpatient, and carrier files were examined for

ICD-9 or CPT procedure codes indicating receipt of liver directed therapy. Procedures included liver resection, liver ablation, and chemoembolization (Table 1). Few patients underwent ablation or chemoembolization; therefore, these categories were combined as "ablative procedures" for all analyses.

Covariates

All patients had stage IV disease at the time of diagnosis. Covariates were defined in Table 1. Sites of metastatic disease were identified using ICD-9 codes for secondary malignant neoplasm (Table 1).

Statistical Analysis

We calculated summary statistics for the overall cohort and determined the percentage of patients receiving chemotherapy, resection of the primary tumor, and liver directed therapy. Chi square tests were used to evaluate the unadjusted associations between liver directed therapy and patient, tumor, and primary treatment characteristics. Multivariate logistic regression was used to determine factors independently associated with the receipt of liver directed therapy. We used a Cochran-Armitage test for trend to evaluate trends in use of chemotherapy, liver resection, liver ablation, liver chemoembolization, and ablation and chemoembolization combined. Disease-specific 5-year survival was calculated for patients in the following treatment groups: overall cohort, patients undergoing liver directed therapy, and those not treated with liver directed therapy. A Kaplan Meier analysis with log rank test was performed to compare survival in patients treated with liver directed therapy vs. those not treated with liver directed therapy during early (2001-2004) and late (2005-2007) time periods.

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 8)

We identified 5,500 patients who received chemotherapy and underwent resection of the primary tumor. 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 (Tables 8 and 9)

Surgical resection was performed in an emergent setting in 20.2% of patients. Modern chemotherapy regimens, those containing oxaliplatin or irinotecan, were used in 56.8% of patients. Standard chemotherapy (5-FU and leucovorin) was administered to 29.1% of patients. The remaining 14.2% of patients received systemic treatment with an agent not specifically identified by our analysis. Bevacizumab was used in 27.9% of patients.

Liver directed therapy, defined as liver resection or an ablative procedure, was performed in 1,918 (34.9%) patients. Liver resection was performed in 30.7% and ablative procedures in 10.1%. Of those receiving liver directed therapy, 16.8% were treated with more than one treatment modality. Over time the rates of liver resection and ablative procedures remained stable, but the use of modern chemotherapy increased from 41.0% in 2001 to 77.3% in 2007, $P<0.0001$. Liver directed therapy was performed

concurrently with resection of the primary tumor in 74.4%, after resection in 21.2%, and before resection in 4.5%.

Factors predicting liver directed therapy (Table 10 and 11)

In a bivariate analysis, younger age, receipt of modern chemotherapy, and use of bevacizumab were associated with a higher likelihood of receiving liver directed therapy. In a multivariable model controlling for comorbidity and economic status, there was a negative association between liver directed therapy and each increasing year (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).

Long-term outcomes following liver directed therapy

Colon cancer was the cause of death in 78.3% of patients. The median survival was 28.4 months for patients undergoing liver-directed therapy compared to 21.1 months in patients who did not have treatment for liver metastases (P<0.0001). Patients with non-cancer related deaths were more likely to be 85 years old or older, have a Charlson comorbidity score of zero, and be treated with a chemotherapy regimen which did not include oxaliplatin or irinotecan; whereas, patients with cancer related deaths were more likely to be 75 years old or older, have colonic primaries, poorly differentiated tumors, have a Charlson comorbidity score of 2 or greater, and have emergency surgery of the primary tumor. Patients diagnosed in the later time period had improved survival compared to those diagnosed in the early time period, regardless of use of liver directed therapy (Figure 7, pg 61).

DISCUSSION

The management of synchronous colorectal cancer liver metastases has evolved over the last decade. We observed that while the use of modern chemotherapeutic regimens increased over time, the use of liver directed therapy remained stable over the study period, and it is scarcely used in older patients presenting with stage IV colorectal cancer. Patients treated with chemotherapy, resection of the primary tumor, and liver directed therapies experienced better 5-year disease specific survival. However, we also observed an improvement over time in survival for all patients, and this was unrelated to the treatment of hepatic metastases.

Our study is the first to document the trends in management of patients with synchronous liver metastases at presentation of colorectal cancer during a time period when newer, more efficacious chemotherapeutic agents were used.

Although prior single institution studies have demonstrated acceptable outcomes in older patients undergoing liver resection for colorectal cancer metastases, these studies were not limited to patients with stage IV disease at initial presentation[44-53] Clinically, synchronous metastases are associated with a worse prognosis than metachronous metastases; therefore, distinguishing outcomes in patients presenting with metastatic disease from those who develop metastases at a later point in time is important.

While our findings support the practice of aggressive treatment of hepatic metastases in appropriately selected patients, we have also observed that overall survival has improved for patients regardless of treatment strategy and despite no increase in the use of liver directed therapy. This suggests that clinicians are better able to select the patients who will benefit most from aggressive therapy, and are avoiding aggressive

interventions in patients unlikely to benefit. Using data from two high-volume cancer referral centers, Kopetz et al. observed a survival improvement for patients with metastatic colorectal cancer diagnosed after 2004, and related this to the adoption of newer, modern chemotherapeutic agents.[22] The value of newer chemotherapeutic agents has been observed in another population-based study.[54] Currently, there are limited data on the effect of increasing age and survival in patients undergoing liver directed therapy.

In our study, younger age, receipt of modern chemotherapy, and use of bevacizumab were the only factors independently associated with receipt of liver directed therapy. Prior studies have also observed that increasing age is associated with decreased utilization of liver directed therapy, particularly liver resection.[11, 55]

Our study has several limitations. Using observational data in cancer patients, there is a significant likelihood of selection bias in comparing patients undergoing different treatment regimens, especially when surgery is considered. However, the primary aim of our study was not to determine the comparative effectiveness of different treatment strategies for these patients. Instead, our primary aim was to document the trends in the use of treatment modalities and survival over time. In addition, our cohort, patients receiving combined treatment for colorectal cancer metastatic to the liver, is 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 all patients with stage IV colorectal cancer. As a result, the external 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.

The treatment of older patients with colorectal cancer liver metastases is challenging, and as a result the ideal treatment algorithm has yet to be developed. As the population ages, the proportion of older patients with colorectal cancer will increase. Our study suggests that practitioners are appropriately selecting younger, healthier patients to undergo aggressive cancer therapy, with improved outcomes over time. Current liver directed therapies need further evaluation in older patients to determine their role, efficacy, and outcomes.

APPENDIX A TABLES

Table 1: ICD-O-3, ICD-9, CPT, and J-codes used to identify colorectal cancer, symptoms, and treatment 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
Symptoms	**Diagnosis codes**
Bleeding/Anemia	569.3, 578.9, 578.1, 280.0, 280.9, 285.1, and 285.9
Perforation	567.9, 567.21, 571.22, 567.3, 567.31, 567.38, 567.39, 569.5, and 569.83
Obstruction	560.89, 560.9, and 569.2
Septic shock	785.52
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 or irinotecan containing regimens)	J9263 or J9206 (in addition to 5FU/LV)
Bevacizumab	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
Ablative 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
Pulmonary resections	CPT: 3220, 3228, 3229, 323, 3230, 3239, 3240, 3241, 3249, 325, 3250, 3259, 326, 329, 19260, 19271, 19272, 32440, 32442, 32445, 32480, 32482, 32484, 32486, 32500, 32503, 32504, 32520, 32522, 32525, 32657, 32663
Site of metastases¥	**ICD-9 diagnosis code**
Liver	197.7
Respiratory (lung, pleura, mediastinum, other respiratory organ)	197.0, 197.1, 197.2, 197.3
Carcinomatosis (small intestine, retroperitoneum/peritoneum, other digestive organs and spleen, disseminated carcinomatosis unspecified site)	197.4, 197.6, 197.8, 199.0
Brain	198.3-198.4
Nodal metastases (lymph nodes of head and neck, intraabdominal, intrathoracic, intrapelvic, lymph nodes of multiple sites, lymph nodes NOS, lymph nodes of inguinal region or lower limb)	196.0, 196.2, 196.1, 196.6, 196.8, 196.9, 196.5

¥ Secondary and unspecified malignant neoplasms

Table 2: Patient and tumor characteristics for older patients with stage IV colorectal cancer by treatment modality, SEER-Medicare 2001-2007 (N=16,168)*

	Overall cohort	Resection of primary tumor only	Chemotherapy only	Resection and chemotherapy	No treatment
Patient Demographics	N=16,168	N=4,435	N=1,792	N=5,500	N=4,441
Age (y), mean ± SD	77.8 ± 7.3	80.0 ± 7.2	75.2 ± 6.1	74.3 ± 5.7	80.8 ± 7.6
Female gender	8,696 (53.8)	2,590 (58.4)	853 (47.6)	2,758 (50.2)	2,495 (56.2)
Race	N=16,142	N=4,424	N=1,790	N=5,495	N=4,432
White	13,380 (82.9)	3,676 (83.1)	1,474 (82.4)	4,666 (84.9)	3,564 (80.4)
Black	1,745 (10.8)	451 (10.2)	200 (11.2)	479 (8.7)	615 (13.9)
Hispanic	324 (2.0)	95 (2.2)	35 (2.0)	109 (2.0)	85 (1.9)
Other	692 (4.3)	202 (4.6)	81 (4.5)	241 (4.4)	168 (3.8)
Charlson Comorbidity Score					
0	9,335 (57.7)	2,330 (52.5)	1,135 (63.3)	3,522 (64.0)	2,348 (52.9)
1	3,828 (23.7)	1,114 (25.1)	388 (21.7)	1,309 (23.8)	1,017 (22.9)
2	1,695 (10.5)	550 (12.4)	162 (9.0)	428 (7.8)	555 (12.5)
≥ 3	1,310 (8.1)	441 (9.9)	107 (6.0)	241 (4.4)	521 (11.7)
Tumor Characteristics					
Type					
Colon cancer	13,491 (83.4)	3,995 (90.1)	1,227 (68.5)	4,532 (82.4)	3,737 (84.2)
Right	5,992 (37.1)	2,058 (46.4)	464 (25.9)	2,181 (39.7)	1,289 (29.0)
Left	4,866 (30.1)	1,427 (32.2)	437 (24.4)	1,868 (34.0)	1,134 (25.5)
Transverse	917 (5.7)	324 (7.3)	59 (3.3)	351 (6.4)	183 (4.1)
Unspecified	1,716 (10.6)	186 (4.2)	267 (14.9)	132 (2.4)	1,131 (25.5)
Rectal cancer	2,677 (16.6)	440 (9.9)	565 (31.5)	968 (17.6)	704 (15.9)
Poorly differentiated	3,883 (24.0)	1,468 (33.1)	272 (15.2)	1,611 (27.3)	532 (12.0)
Liver resection	2,846 (17.6)	1,025 (23.1)	48 (2.7)	1,686 (30.7)	87 (2.0)

*All data are expressed as N and % unless otherwise noted

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Table 3: Logistic regression analysis of factors associated with resection of primary tumor, TCR/SEER-Medicare 2001-2007 (N=16,168)*

	Odds Ratio (95% CI)	Unadjusted Odds Ratio (95% CI)
Diagnosis year (continuous)	0.97 (0.95-0.99)	0.97 (0.95-0.98)
Age group (ref: 66-69)		
70 - 74	0.91 (0.81-1.02)	0.93 (0.83-1.04)
75 - 79	0.75 (0.67-0.84)	0.78 (0.70-0.87)
80 - 84	0.59 (0.52-0.66)	0.61 (0.55-0.69)
>= 85	0.44 (0.39-0.49)	0.44 (0.39-0.49)
Sex (ref: Female)		
Male	0.92 (0.85-0.98)	1.00 (0.94-1.07)
Race (ref: White)		
Black	0.68 (0.60-0.76)	0.70 (0.63-0.77)
Hispanic	1.08 (0.84-1.39)	1.04 (0.83-1.31)
Other	1.04 (0.87-1.23)	1.08 (0.92-1.27)
Charlson Comorbidity (ref: 0)		
1	1.08 (0.99-1.18)	1.03 (0.95-1.11)
2	0.89 (0.79-1.00)	0.81 (0.73-0.90)
≥ 3	0.71 (0.62-0.81)	0.64 (0.57-0.72)
Cancer site (ref: rectum)		
Right	2.31 (2.09-2.55)	2.19 (1.99-2.40)
Left	2.07 (1.87 (2.29)	1.90 (1.73-2.10)
Transverse	2.67 (2.25-3.17)	2.52(2.14-2.98)
Unspecified	0.26 (0.22-0.30)	0.21 (0.18-0.24)
Differentiation		
Poorly differentiated	2.55 (2.33-2.79)	3.03 (2.78-3.31)

***Model also adjusted for education quartile**

Table 4: Cox proportional hazards model evaluating five-year disease specific survival for all patients diagnosed with stage IV colorectal cancer.

	All patients N=16,168 Hazards Ratio
Diagnosis year (continuous)	0.96 (0.95-0.97)
Age group (ref: 66-69)	
70 - 74	1.12 (1.05-1.19)
75 - 79	1.16 (1.09-1.23)
80 - 84	1.19 (1.11-1.27)
>= 85	1.24 (1.15-1.32)
Sex (ref: Female)	
Male	0.95 (0.92-0.99)
Race (ref: White)	
Black	0.99 (0.93-1.05)
Hispanic	0.94 (0.82-1.08)
Other	0.86 (0.78-0.94)
Education (ref: Q1)	
Q2	0.97 (0.92-1.02)
Q3	0.96 (0.91-1.02)
Q4	0.96 (0.91-1.01)
Charlson Comorbidity (ref: 0)	
1	1.04 (0.99-1.08)
2	1.08 (1.01-1.15)
≥3	1.11 (1.03-1.19)
Cancer site (ref: rectum)	
Colon	1.17 (1.12-1.23)
Differentiation (ref: well/moderately differentiated and other)	
Poorly differentiated	1.38 (1.32-1.44)
Primary resection (ref: No resection)	
Emergency	0.56 (0.53-0.59)
Elective	0.43 (0.41-0.45)
Chemotherapy regimen (ref: No chemotherapy)	
Standard	0.42 (0.39-0.44)
Modern	0.42 (0.39-0.44)
Other regimen	0.46 (0.42-0.49)
Bevacizumab (ref: No)	0.82 (0.76-0.88)
Metastasectomy (ref: No)	1.03 (0.98-1.09)

Table 5: Patient, tumor, and treatment characteristics of patients presenting with stage IV colorectal cancer. N=7,738.

	Overall cohort
Patient Demographics	
Age (y), mean ± SD	77.7 ± 7.2
Female gender	4,164 (53.8)
Race	N=7,725
White	6,482 (83.9)
Black	750 (9.7)
Hispanic	155 (2.0)
Other	338 (4.4)
Charlson Comorbidity Score	
0	4,482 (57.9)
1	1,849 (23.9)
2	812 (10.5)
≥ 3	595 (7.7)
Tumor Characteristics	
Type	
Colon cancer	6,297 (81.4)
Right	3,024 (39.1)
Left	2,318 (30.0)
Transverse	476 (6.2)
Unspecified	479 (6.2)
Rectal cancer	1,441 (18.6)
Poorly differentiated	2,152 (27.8)
Treatment Characteristics	
Chemotherapy	3,303 (42.7)
Standard	901 (27.3)
Modern	1,791 (54.2)
Other	611 (18.5)
Resection of the primary tumor	5,946 (76.8)
First treatment modality	
Chemotherapy	2,276 (29.4)
Colon cancer	1,450 (23.0)
Rectal cancer	826 (57.3)
Resection of the primary tumor	5,462 (70.6)
Colon cancer	4,847 (77.0)
Rectal cancer	615 (42.7)
Metastasectomy	1,559 (20.2)

Table 6: Bivariate analysis comparing the chemotherapy group vs. the resection group.

	Chemotherapy group	Resection of primary tumor group	p-value
Patient Demographics	N=2,276	N=5,462	
Age			<.0001
66-69 yrs	530 (23.3%)	655 (12.0%)	
70-74 yrs	635 (27.9%)	1,013 (18.6%)	
75-79 yrs	599 (26.3%)	1,227 (22.5%)	
80-84 yrs	357 (15.7%)	1,254 (23.0%)	
≥ 85 yrs	155 (6.8%)	1,313 (24.0%)	
Female gender	1,087 (47.8%)	3,077 (56.3%)	<.0001
Race (N=7,725)			NS
White	1,892 (83.2%)	4,590 (84.2%)	
Black	234 (10.3%)	516 (9.5%)	
Hispanic	49 (2.2%)	106 (1.9%)	
Other	99 (4.4%)	239 (4.4%)	
Charlson Comorbidity Score			<.0001
0	1,460 (64.2%)	3,022 (55.3%)	
1	505 (22.2%)	1,344 (24.6%)	
2	190 (8.4%)	622 (11.4%)	
≥ 3	121 (5.3%)	474 (8.7%)	
Tumor Characteristics			
Type			<.0001
Colon cancer	1,450 (63.7%)	4,847 (88.7%)	
Right	551 (24.2%)	2,473 (45.3%)	
Left	546 (24.0%)	1,772 (32.4%)	
Transverse	71 (3.1%)	405 (7.4%)	
Unspecified	282 (12.4%)	197 (3.6%)	
Rectal cancer	826 (36.3%)	615 (11.3%)	
Poorly differentiated	374 (16.4%)	1,778 (32.6%)	<.0001
Carcinomatosis	797 (35.0%)	2,094 (38.3%)	.0059
Liver metastases	1,909 (83.9%)	3,747 (68.6%)	<.0001
Pulmonary metastases	1,103 (48.5%)	1,297 (23.8%)	<.0001
Treatment			
Chemotherapy			<.0001
Standard	609 (26.8%)	292 (5.4%)	
Modern	1,177 (51.7%)	614 (11.2%)	
Other	490 (21.5%)	121 (2.2%)	
None	N/A	4,435 (81.2%)	
Metastasectomy (yes)	194 (8.5%)	1,365 (25.0%)	<.0001

Table 7: Cox proportional hazards model evaluating 3-year disease specific survival in older patients undergoing treatment for stage IV colorectal cancer (N=7,738).

Factor (REF)	**Hazard Ratio (95% CI)**
First treatment modality - chemotherapy (resection)	0.90 (0.84-0.95)
Year of diagnosis	0.95 (0.94-0.96)
Age (66-69 yrs)	
70-74 yrs	1.20 (1.10-1.32)
75-79 yrs	1.26 (1.16-1.38)
80-84 yrs	1.38 (1.26-1.51)
≥ 85 yrs	1.60 (1.46-1.76)
Female sex (male)	1.02 (0.97-1.07)
Race (White)	
Black	1.14 (1.05-1.25)
Hispanic	1.06 (0.88-1.27)
Other	0.94 (0.82-1.07)
Charlson comorbidity score (0)	
1	1.04 (0.97-1.10)
2	1.09 (0.99-1.19)
≥ 3	1.29 (1.17-1.44)
Cancer type - colon (rectal)	1.19 (1.11-1.27)
Metastasectomy (yes)	1.07 (1.01-1.15)

Table 8: Patient, tumor, and treatment characteristics of older adults with stage IV colorectal cancer treated with chemotherapy and resection of the primary tumor, TCR-Medicare 2001-2007 (N = 5,500).

Patient Demographics	**N (%)**
Age (y), mean ± SD	74.3 ± 5.7
Female gender	2,758 (50.2%)
Race (N=2521)	
White	4,666 (84.9%)
Black	479 (8.7%)
Hispanic	109 (2.0%)
Other	241 (4.4%)
Charlson Comorbidity Score	
0	3,522 (64.0%)
1	1,309 (23.8%)
2	428 (7.8%)
3	241 (4.4%)
Tumor Characteristics	
Type	
Colon cancer	4,532 (82.4%)
Rectal cancer	968 (17.6%)
Differentiation	
Poorly differentiated	1,611 (29.3%)
Site	
Right	2,181 (39.7%)
Left	1,868 (34.0%)
Transverse	351 (6.4%)
Unspecified	132 (2.4%)
Chemotherapy regimen	
Modern chemotherapy	3,123 (56.8%)
Standard chemotherapy	1,599 (29.1%)
Unknown chemotherapy	778 (14.2%)
Surgical resection	
Emergency resection	1,109 (20.2%)
Elective resection	4,391 (79.8%)
Liver directed therapy	
Resection	1,686 (30.7%)
Ablative procedure	554 (10.1%)

Table 9: Liver directed therapy in older patients with stage IV colorectal cancer (N=5,500)*

Resection	Chemotherapy	Liver resection	Ablation	Chemoembolization	N (%)
Yes	Yes	Yes	Yes	Yes	27 (0.5%)
Yes	Yes	Yes	Yes	No	258 (4.7%)
Yes	Yes	Yes	No	Yes	37 (0.7%)
Yes	Yes	Yes	No	No	1,364 (24.8%)
Yes	Yes	No	Yes	Yes	23 (0.4%)
Yes	Yes	No	Yes	No	139 (2.5%)
Yes	Yes	No	No	Yes	70 (1.3%)
Yes	Yes	No	No	No	3,582 (65.1%)

* 16.8% of patients were treated with more than one type of liver directed therapy

Table 10: Bivariate analysis of factors associated with liver directed therapy in older adults with stage IV colorectal cancer, TCR-Medicare 2001-2007

	Liver directed therapy N=1,918	p-value	Resection N=1,686	p-value	Ablation/ chemoembolization N=554	p-value
Age (yrs)		<.0001		<.0001		<.0001
66-69	516 (26.9%)		452 (26.8%)		169 (30.5%)	
70-74	611 (31.9%)		547 (32.4%)		189 (34.1%)	
75-79	489 (25.5%)		425 (25.2%)		119 (21.5%)	
80-84	229 (11.9%)		202 (12.0%)		60 (10.8%)	
85+	73 (3.8%)		60 (3.6%)		17 (3.1%)	
Race		NS		NS		NS
White	1,648 (85.9%)		1,449 (85.9%)		480 (86.6%)	
Black	163 (8.5%)		144 (8.5%)		43 (7.8%)	
Hispanic	35 (1.8%)		32 (1.9%)		7 (1.3%)	
Other	72 (3.8%)		61 (3.6%)		24 (4.3%)	
Cancer type		NS		NS		0.003
Colon	1,561 (81.4%)		1,386 (82.2%)		431 (77.8%)	
Rectum	357 (18.6%)		300 (17.8%)		123 (22.2%)	
Emergency surgery		NS		NS		0.001
Yes	368 (19.2%)		335 (19.9%)		83 (15.0%)	
No	1,550 (80.8%)		1,351 (80.1%)		471 (85.0%)	
Chemotherapy		<.0001		<.0001		<.0001
Standard	478 (24.9%)		427 (25.3%)		120 (21.7%)	
Modern	1,197 (62.4%)		1,050 (62.3%)		364 (65.7%)	
Other	243 (12.7%)		209 (12.4%)		70 (12.6%)	
Bevacizumab		<.0001		0.005		<.0001
Yes	602 (31.4%)		514 (30.5%)		199 (35.9%)	

51

No	1,316 (68.6%)		1,172 (69.5%)		355 (64.1%)	

Table 11: Multivariate analysis of factors predicting 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)		
Modern	1.44	1.25-1.66
Other	1.11	0.92-1.35

APPENDIX B FIGURES

Figure 1. Cohort selection for patients in the Texas Cancer Registry (TCR) and Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data diagnosed with stage IV colorectal cancer.

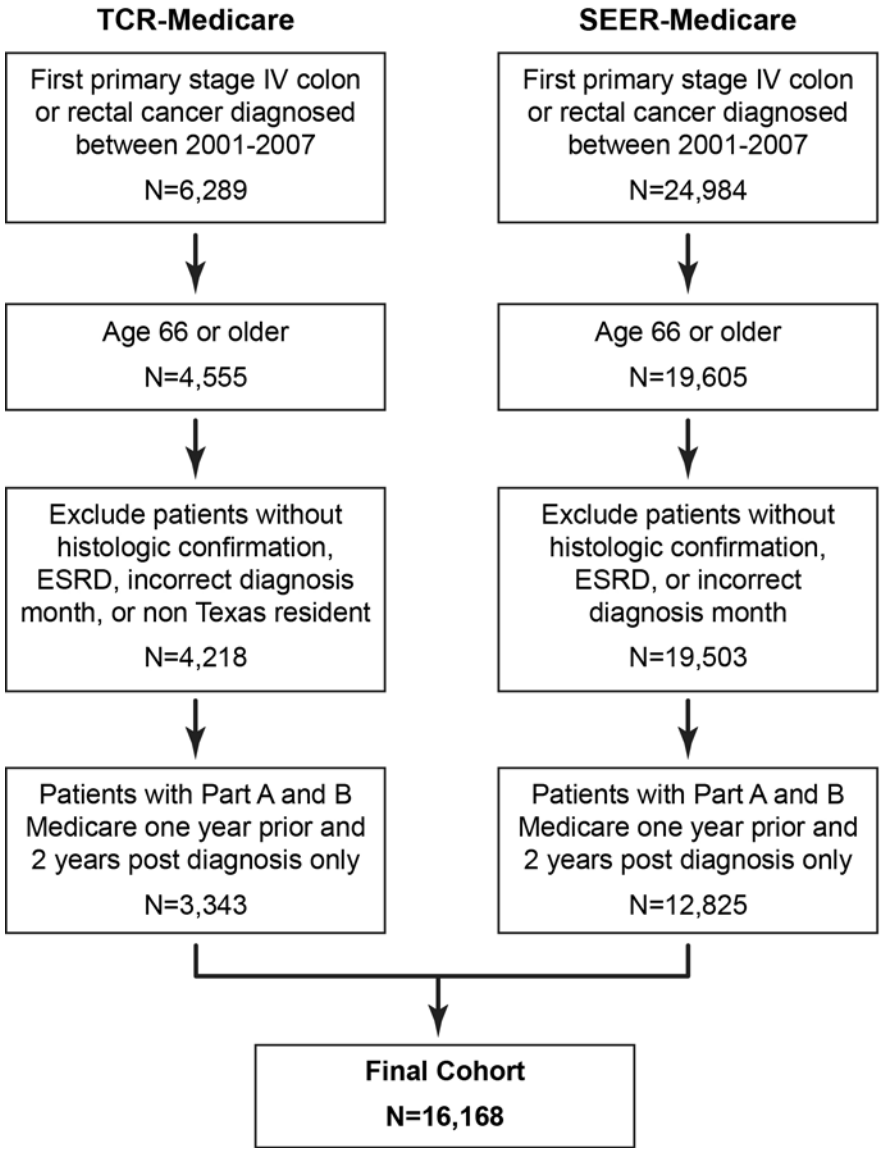
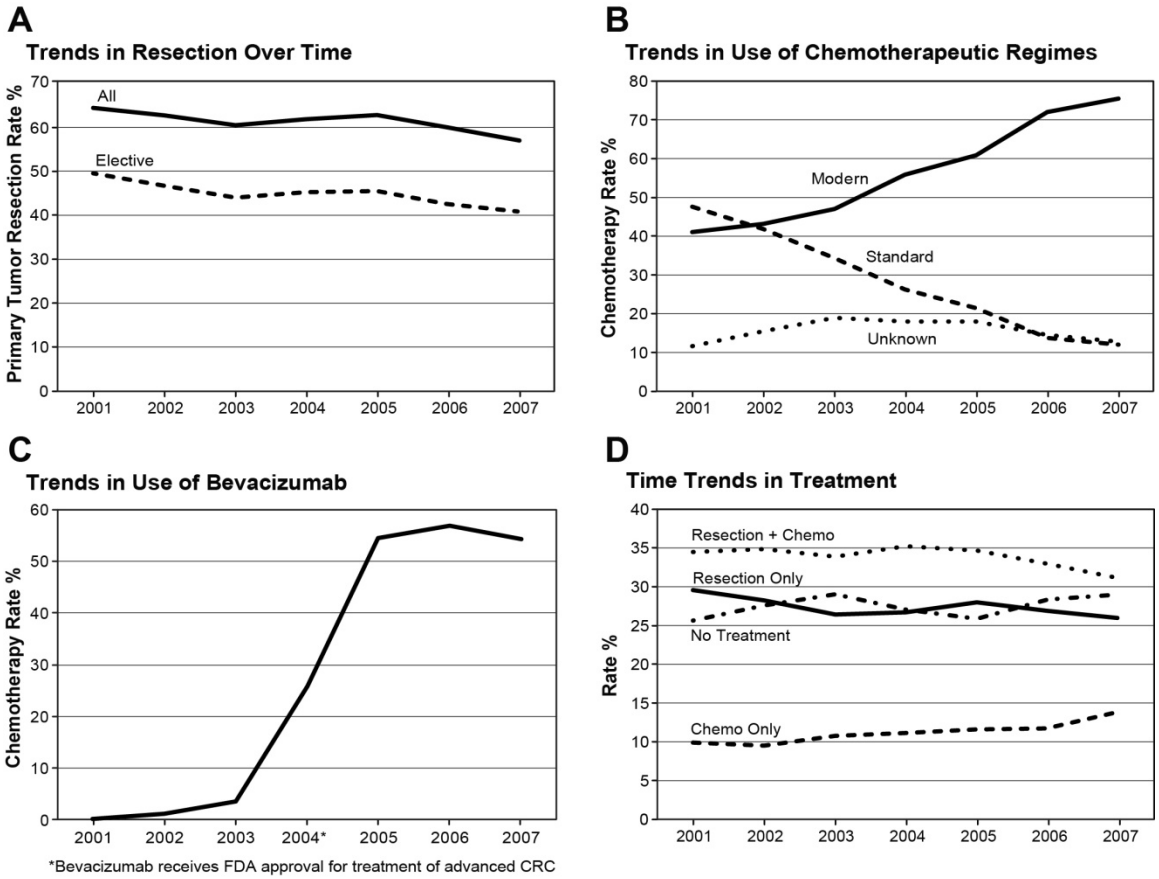


Figure 2 A. Time trends in resection of the primary tumor for the overall cohort and elective resection of the primary tumor. B. Trends in use of standard, modern, and other chemotherapeutic regimens in patients with stage IV colorectal cancer. C. Trends in use of bevacizumab in older patients presenting with stage IV colorectal cancer. D. Time trends in treatments.



A. Time trends (2001-2007) in resection of the primary tumor for the overall cohort (N=9,935, solid line), elective resection of the primary tumor (N=7,274, dotted line). B. Trends in use of standard, modern, and other chemotherapeutic regimens in patients with stage IV colorectal cancer. Solid line = modern chemotherapy; Dashed line = standard chemotherapy; Dotted line = other chemotherapy. C. Trends in use of bevacizumab in older patients presenting with stage IV colorectal cancer. D. Time trends in treatments. Solid line = resection of primary tumor only; Dashed line = chemotherapy only; Dotted line = chemotherapy and resection of primary tumor; Dot and dash line = no treatment.

Figure 3. Cohort selection. TCR- and SEER-Medicare linked data for patients presenting with stage IV colorectal cancer.

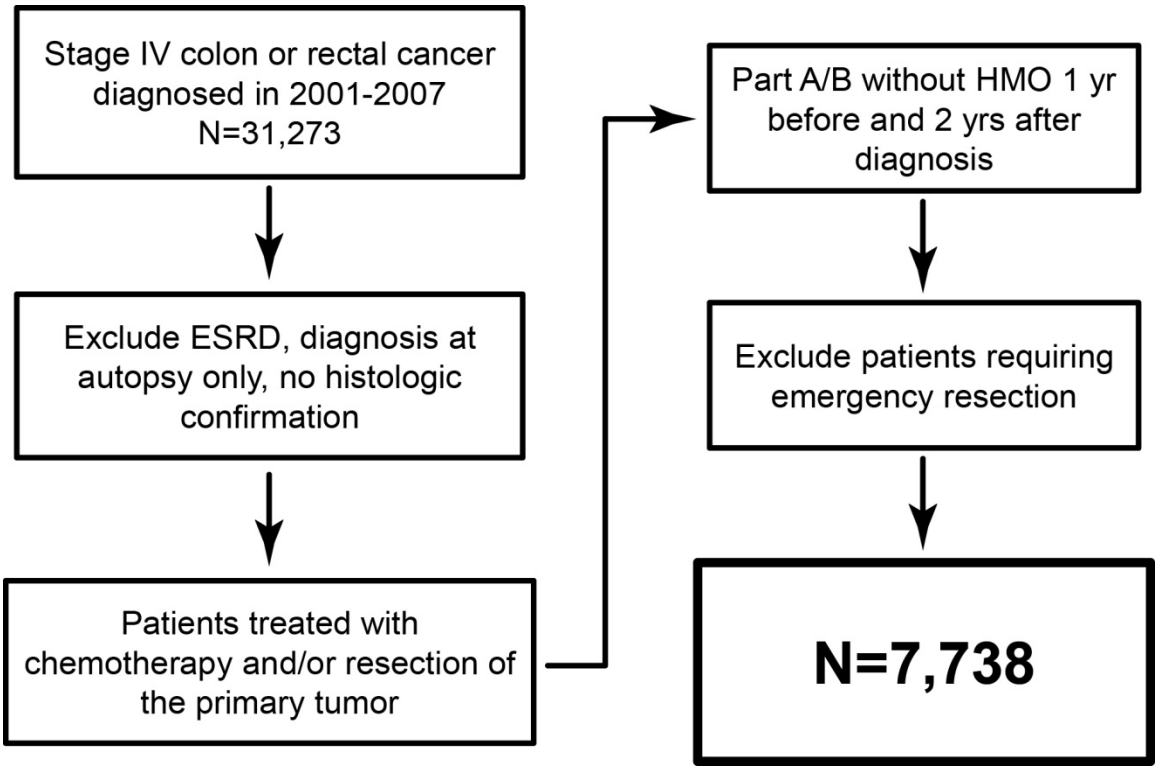


Figure 4. Treatment classification for all patients undergoing treatment for stage IV colorectal cancer.

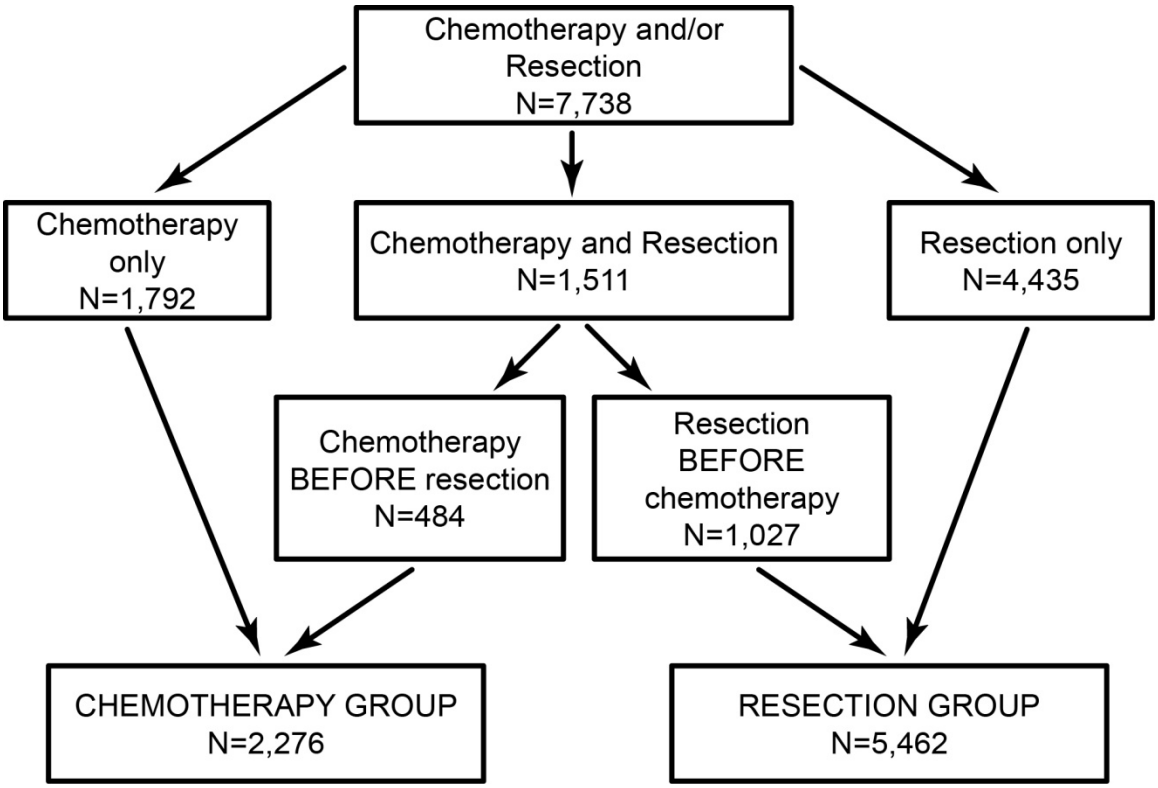


Figure 5. Time trend in the use of chemotherapy as the initial treatment modality.

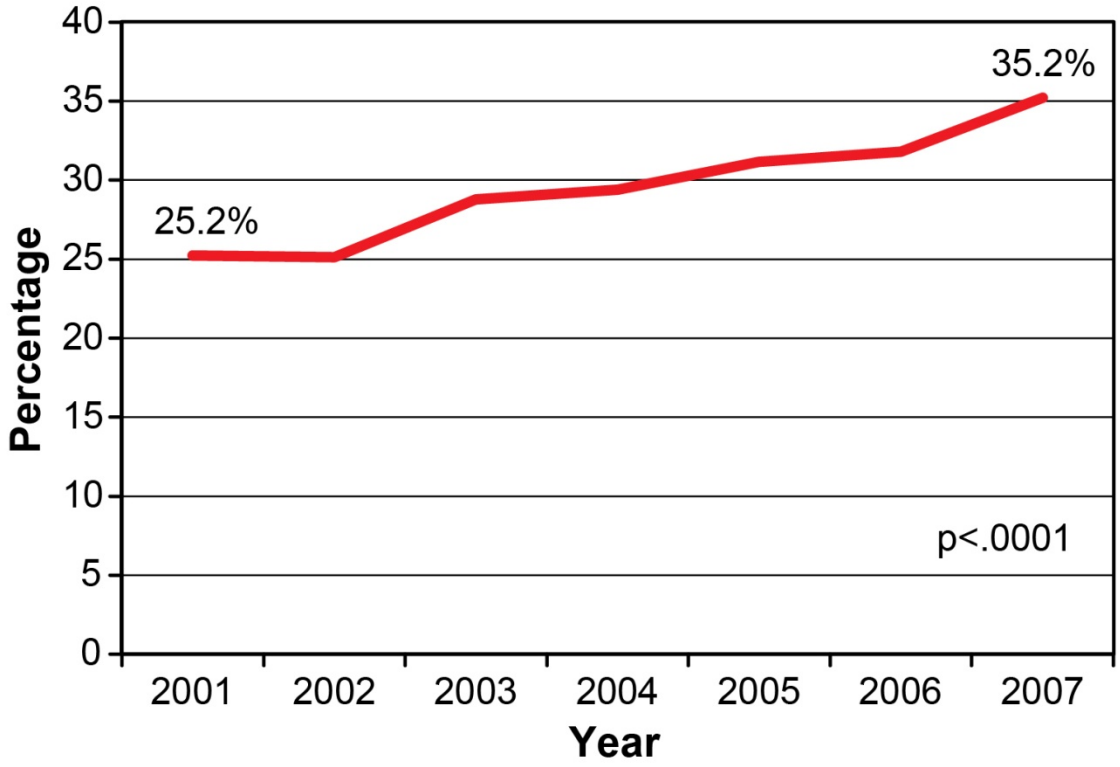
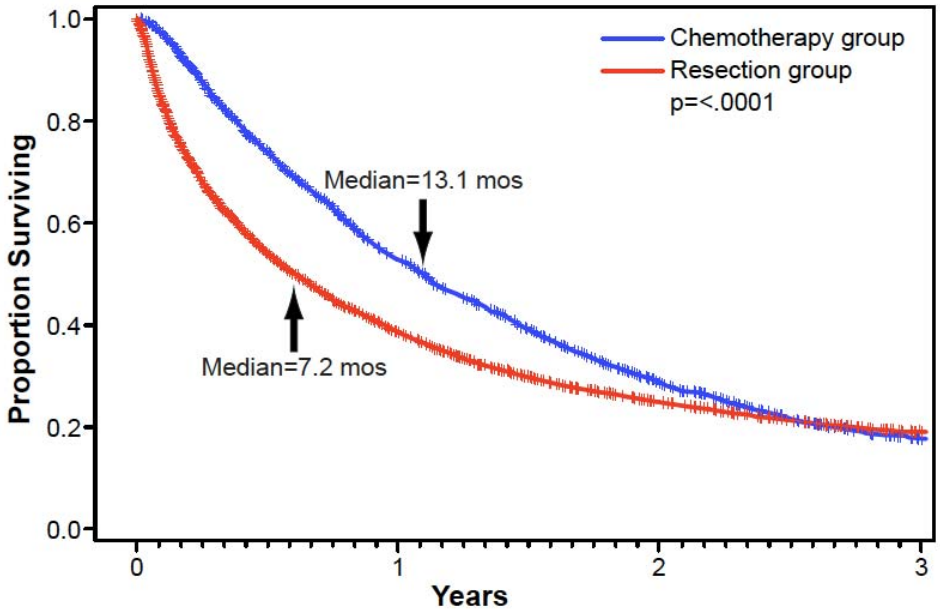


Figure 6. A) Kaplan-Meier survival analysis for all patients. B) Kaplan-Meier survival analysis for patients treated with both chemotherapy and surgical resection of the primary tumor.

A.



B

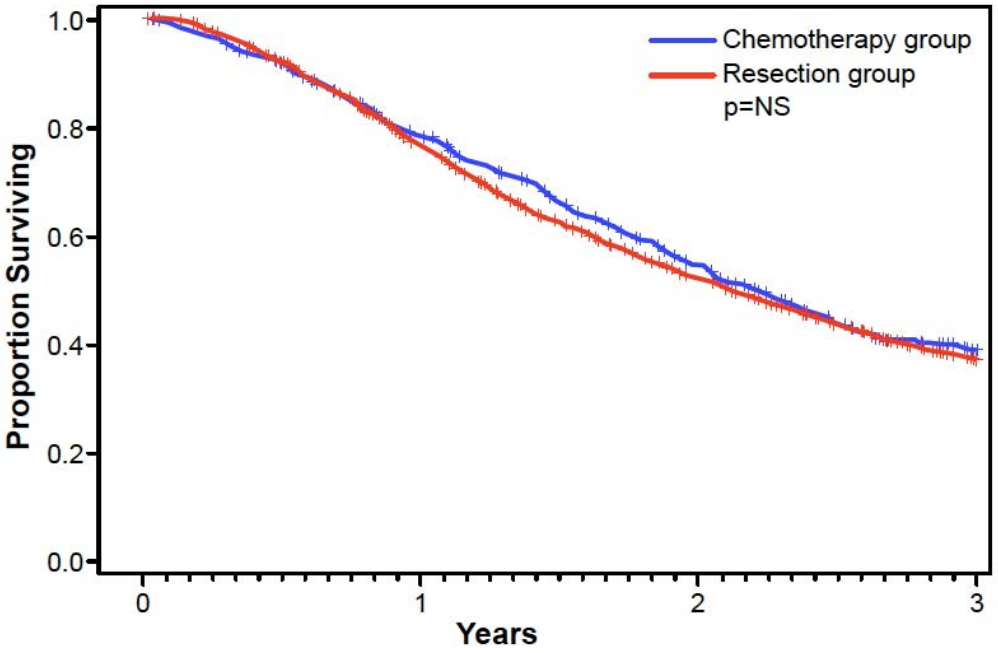
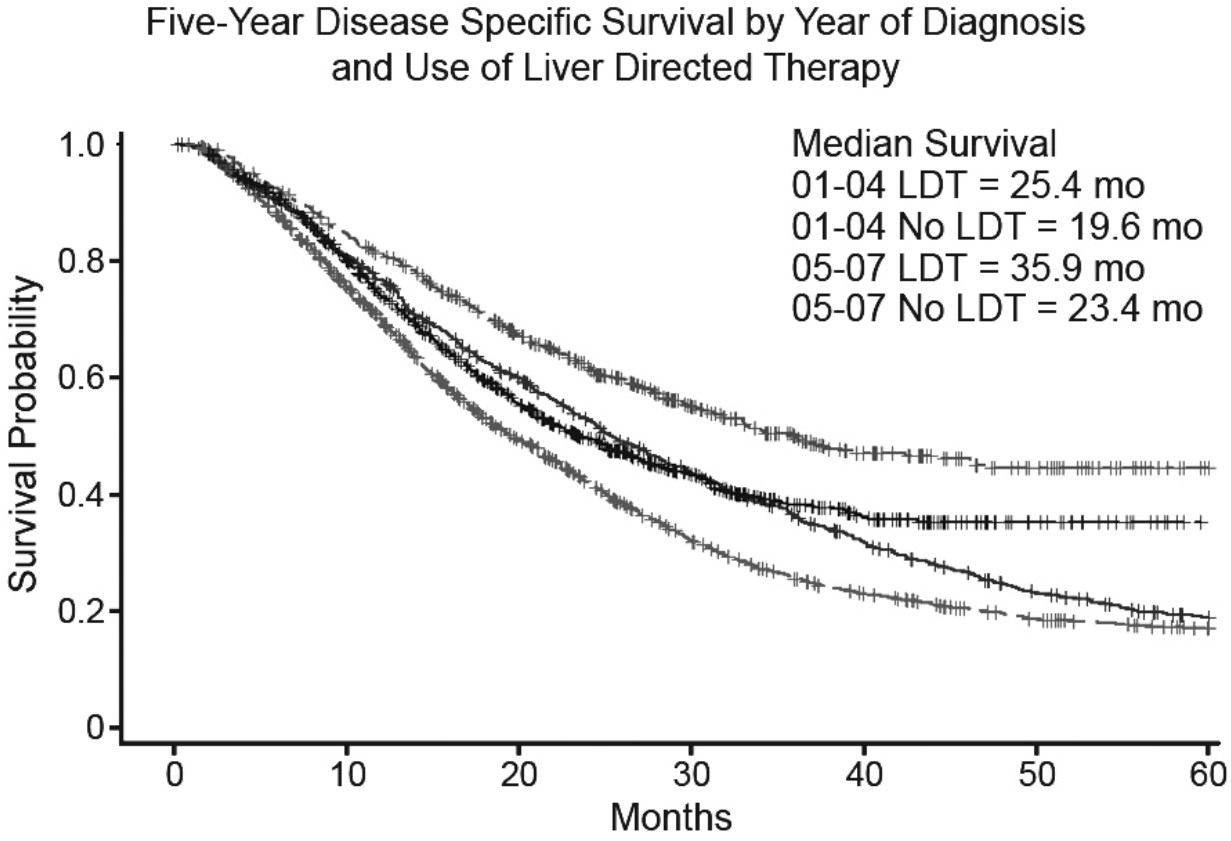


Figure 7. Five-year disease specific survival in early and late time periods by treatment.



All patients were treated with resection of the primary tumor and chemotherapy;
— 01-04 LDT; — 01-04 No LDT; — 05-07 LDT; — 05-07 No LDT;
LDT = liver directed therapy; $P < 0.0001$.

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