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ORIGINAL REPORT

Improved Survival in Metastatic Colorectal Cancer Is Associated With Adoption of Hepatic Resection and Improved Chemotherapy

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ABSTRACT

Purpose
Fluorouracil/leucovorin as the sole therapy for metastatic colorectal cancer (CRC) provides an overall survival of 8 to 12 months. With an increase in surgical resections of metastatic disease and development of new chemotherapies, indirect evidence suggests that outcomes for patients are improving in the general population, although the incremental gain has not yet been quantified.

Methods
We performed a retrospective review of patients newly diagnosed with metastatic CRC treated at two academic centers from 1990 through 2006. Landmark analysis evaluated the association of diagnosis year and liver resection with overall survival. Additional survival analysis of the Surveillance Epidemiology and End Results (SEER) database evaluated a similar population from 1990 through 2005.

Results
Two thousand four hundred seventy patients with metastatic CRC at diagnosis received their primary treatment at the two institutions during this time period. Median overall survival for those patients diagnosed from 1990 to 1997 was 14.2 months, which increased to 18.0, 18.6, and 29.3 months for patients diagnosed in 1998 to 2000, 2001 to 2003, and 2004 to 2006, respectively. Likewise, 5-year overall survival increased from 9.1% in the earliest time period to 19.2% in 2001 to 2003. Improved outcomes from 1998 to 2004 were a result of an increase in hepatic resection, which was performed in 20% of the patients. Improvements from 2004 to 2006 were temporally associated with increased utilization of new chemotherapeutics. In the SEER registry, overall survival for the 49,459 identified patients also increased in the most recent time period.

Conclusion
Profound improvements in outcome in metastatic CRC seem to be associated with the sequential increase in the use of hepatic resection in selected patients (1998 to 2006) and advancements in medical therapy (2004 to 2006).

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INTRODUCTION

When fluorouracil (FU) and leucovorin were the sole therapeutic options, the median overall survival times for patients with metastatic colorectal cancer (CRC) were stagnant, at approximately 8 to 12 months.[1] US Food and Drug Administration approval of irinotecan, oxaliplatin, capecitabine, bevacizumab, cetuximab, and panitumumab for metastatic CRC have increased treatment options beyond previously used regimens containing FU and leucovorin. Recent published phase III trials of combination regimens in patients with previously untreated metastatic CRC have demonstrated substantial improvements in overall survival, with median overall survival times now ranging between 18 and 24 months with combination regimens (Fig 1; details on methods and references can be found in the Appendix, online only). Recent studies suggest that survival continues to improve with the routine inclusion of biologic agents, although the degree of benefit seems to vary based on regimen and patient selection.[2-5]

A second development in these patients is the increased recognition that surgically resecting liver-limited metastases may substantially improve long-term outcomes.[6] Liver metastases occur in approximately 30% of all CRC patients and account for at least two thirds of CRC deaths.[7,8] The definition of resectable liver metastases has changed

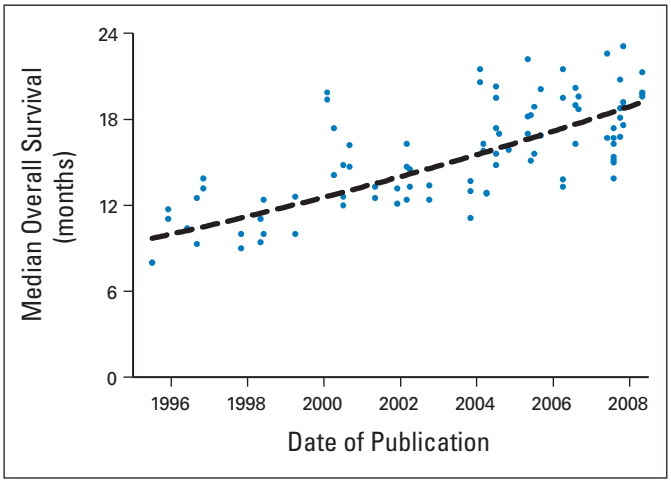

Fig 1. Median overall survival of previously untreated patients with metastatic colorectal cancer reported in published phase III trials since 1995.

over the years, now focusing on the resection of all visible liver metastases while preserving at least a 20% to 25% liver remnant with adequate vascular supply and biliary drainage, with the expectation that such a resection would render the patient free of radiographically evident disease.[7] It has been estimated that 20% to 30% of patients with liver metastases are potential candidates for this approach. Retrospective studies in patients who undergo complete surgical resection suggest overall survival rates that exceed 50% at 5 years and range from 17% to 25% at 10 years.[6,7] Although these retrospective studies have been criticized for suffering from selection bias,[9] they demonstrate that long-term survival is possible in a select group of patients with metastatic disease.

Taken together, the incremental improvements in survival for patients on phase III trials and excellent outcomes after hepatic resection in surgical series represent only indirect evidence of improvements in outcomes for the broader population of patients with metastatic CRC. Reports from population-based studies are lacking. Thus, the purpose of this study is to evaluate the changes in survival of patients with metastatic CRC using both multi-institutional and population-based databases and to associate these changes to hepatic resection utilization and temporal trends in improvements in chemotherapy.

METHODS

Institutional Patient Identification

Adult patients diagnosed with metastatic CRC were identified from the tumor registries at The University of Texas M. D. Anderson Cancer Center (M. D. Anderson) in Houston, TX, and the Mayo Clinic in Rochester, MN. Patients of interest were diagnosed between January 1, 1990, and December 31, 2006, with follow-up through July 31, 2008. Only patients with adenocarcinomas of the colon and rectum and with synchronous metastatic disease at the time of initial diagnosis of CRC were included to minimize any influence of adjuvant treatment. Separate surgical databases were used to identify patients who subsequently underwent partial hepatic resection, defined as either anatomic or nonanatomic resection of liver metastases with the goal of rendering the patient free of visible tumor. To minimize referral bias for liver resection, patients were included only if they received chemotherapy, radiation, and/or resection of the primary tumor at one of the two institutions, thereby excluding patients presenting solely for consultations or hepatic resection.

Demographic and disease information was entered into the tumor registry by coding staff, with verification of disease site, histology, and stage performed by a second coder for all patients. Vital status was ascertained through clinical follow-up, searches of administrative death indices, and follow-up letters to patients by the respective tumor registries. Trends in chemotherapy administration for this study population were determined from the respective institutional pharmacy databases. The relative number of patients with metastatic CRC treated with a given chemotherapy agent in a particular year was determined by normalizing the absolute number of patients treated per year by the number of such patients treated with irinotecan in 1998 and the volume of new patients with metastatic CRC treated during the particular year. To verify the tumor registry and hepatic resection data, we manually reviewed a random 5% sample of individual records to confirm the presence of metastatic disease, tumor histology, diagnosis date, vital status, and history of liver resection.

Surveillance, Epidemiology, and End Results Registry Patient Identification

Data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER), a population-based cancer registry, were used for this study.[10] SEER registry patients eligible for this study included adults with stage IV (American Joint Committee on Cancer sixth edition) adenocarcinoma of the colon diagnosed from January 1990 through December 2005. Patients were excluded for lack of histologic confirmation, history of prior malignancy, or cancer reporting source identified as a nursing home, hospice, autopsy, or death certificate. The SEER registry routinely collects data on patient demographics, histology, disease stage at diagnosis, and primary site surgery. SEER does not collect data on chemotherapy or surgery to resect metastatic disease, which was therefore not examined in this analysis.

Statistical Analysis

Survival curves were generated using the Kaplan-Meier method, with comparisons between groups performed using the log-rank test. For analysis of the impact of hepatic resection on survival, the length of survival will impact the possibility that patients will undergo hepatic resection, thereby inducing a bias in favor of resection using traditional survival methods. Therefore, a landmark analysis was used to minimize the bias induced by including events that occur after the baseline time in hazard models.[11,12] This analysis included patients who were alive at 12 months after diagnosis (the landmark time as determined a priori) and compared the outcomes of patients who had and had not undergone resection in the prior 12 months. A multivariate landmark analysis by Cox regression was subsequently performed to evaluate the impact of resection after controlling for year of diagnosis. To evaluate the factors other than surgery on outcomes, survival curves were again generated with the Kaplan-Meier method after censoring patients who underwent hepatic resection at the time of their surgery, as has been previously described.[11]

For the most recent time period, estimates of 5-year overall survival were generated from the proportional hazards model by applying the hazard ratio and its 95% CI for the 2004 to 2006 time period to the baseline cumulative hazard of the entire population. All analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL), STATA version 10.0 (release 2007; STATA, College Station, TX), and GraphPad Prism version 5.01 (GraphPad; La Jolla, CA). A two-sided $P < .05$ was considered significant. This study was approved by both the M. D. Anderson and Mayo Clinic Institutional Review Boards.

RESULTS

A total of 2,470 patients (856 from Mayo Clinic; 1,614 from M. D. Anderson) with metastatic CRC were treated at the two institutions

during the 17-year period from 1990 through 2006. There was concordance between the registry databases and clinical records in more than 99% of patients for demographics, date of diagnosis, history of liver resection, and vital status, and 96% of patients for the presence of metastatic disease. The majority of patients incorrectly identified as metastatic in the registries were patients with unresectable, locally advanced disease.

The median age, histology, location of the primary tumor, and gender distribution of the population were unchanged over the time period evaluated. There were no differences in overall survival outcomes between the two institutions (hazard ratio [HR], 1.03, $P = .58$).

There was no significant difference in the median overall survival times from 1990 through 1997 ($P > .05$ for comparisons of 1990 to 1991, 1992 to 1994, and 1995 to 1997), and therefore, these time periods were pooled, with a median overall survival time of 14.2 months (95% CI, 13.3 to 15.2 months). In contrast to the lack of improvement between 1990 and 1997, significant improvements were seen in the later periods ($P < .05$ for all comparisons to 1990 to 1997). During these later periods, median overall survival times were 18.0 months (95% CI, 15.8 to 20.2 months), 18.6 months (95% CI, 16.4 to 20.8 months), and 29.2 months (95% CI, 24.3 to 34.2 months) for 1998 to 2000, 2001 to 2003, and 2004 to 2006, respectively (Fig 2). Likewise, the 5-year overall survival rate increased from 9.1% for patients diagnosed in 1990 through 1997 to 13.0% for those diagnosed in 1998 through 2000 and 19.2% for those diagnosed in 2001 through 2003; 5-year overall survival is not yet available for those diagnosed from 2004 through 2006. Proportional hazards modeling of the survival curves for patients diagnosed in 2004 through 2006 predicts a 32% 5-year survival rate (95% CI, 27% to 38%).

Two hundred thirty-one patients underwent hepatic resection. Beginning with patients diagnosed in 1998, hepatic resections were performed with increasing frequency (Fig 3A). From 2000 through 2006, the proportion of metastatic CRC patients who underwent hepatic resection remained unchanged at approximately 20% of the population.

Landmark analysis was used to evaluate the impact of hepatic resection on survival. A 12-month landmark was chosen, at which point 85% of the liver resections had been performed and 70% of the population remained alive (the timing of these resections is shown in Appendix Fig A1, online only). For patients diagnosed in 1998 through 2006 who were alive 12 months after diagnosis, the 5-year survival rate for patients who had previously undergone hepatic resection was 55.2%, compared with 19.5% for patients who had unresected disease during the same time period; median overall survival time for these two groups was 65.3 months (95% CI, 51.6 to 70.6 months) and 26.7 months (95% CI, 24.9 to 28.6 months), respectively (Fig 3B). After controlling for the impact of the date of diagnosis on survival, a history of hepatic resection was associated with an HR of 0.35 (95% CI, 0.27 to 0.44; $P < .001$).

To estimate the impact of changes in chemotherapy treatments and to exclude the effects of hepatic resections, overall survival analyses were repeated after censoring patients with hepatic resection at the time of surgery. Compared with patients diagnosed before 1998, overall survival for patients who did not undergo hepatic resection did not improve from the period of 1998 through 2000 (HR, 0.89; 95% CI, 0.80 to 1.01; $P = .06$) and minimally improved in the period of 2001 through 2003 (HR, 0.87; 95% CI, 0.76 to 0.98; $P = .03$; Fig 4). In distinct contrast, patients diagnosed between 2004 and 2006 had a significant improvement in their overall survival, with an HR of 0.53 (95% CI, 0.45 to 0.62; $P < .001$). Review of institutional pharmacy

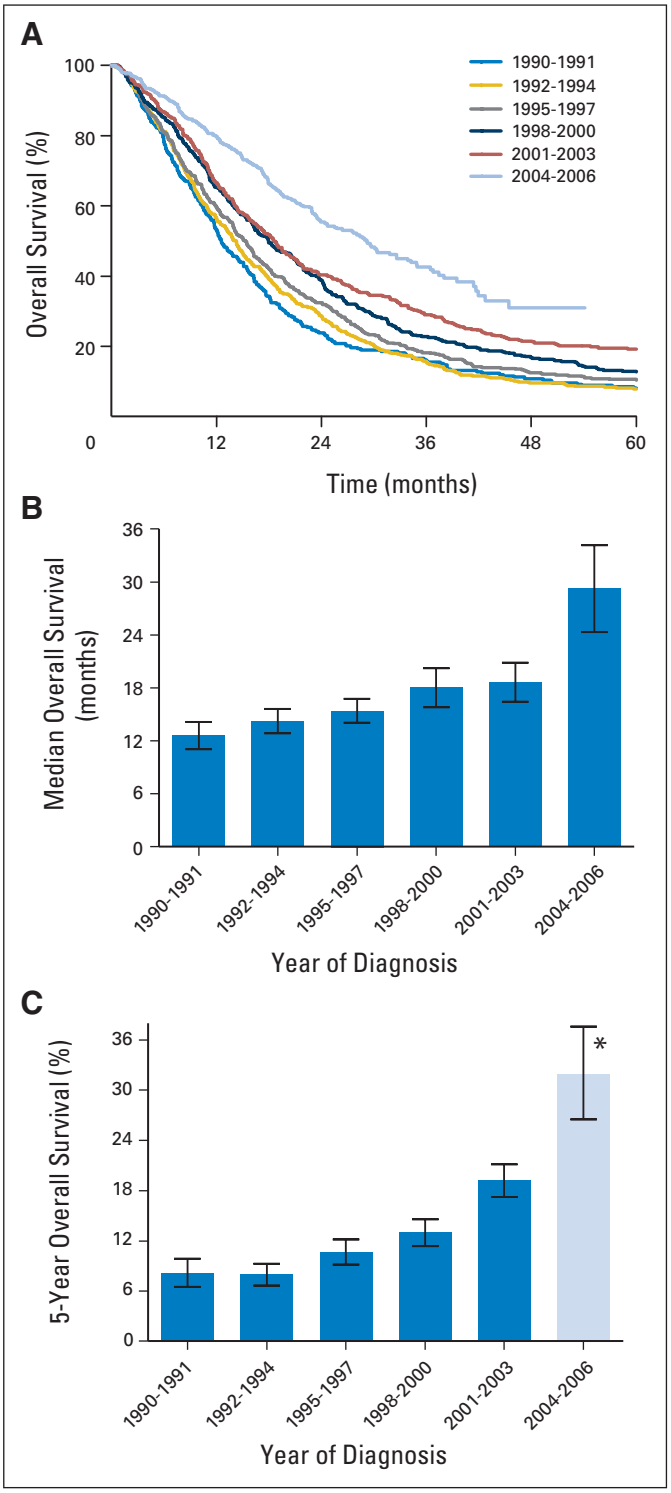

Fig 2. Overall survival for patients with metastatic colorectal cancer treated at The M.D. Anderson Cancer Center and the Mayo Clinic by year of diagnosis. (A) Kaplan-Meier curve. (B) Median overall survival. Error bars represent 95% CIs. (C) Five-year overall survival. Error bars represent SEM. (*) For 2004 to 2006, this represents a statistical projection of 5-year overall survival (error bars represent 95% CI).

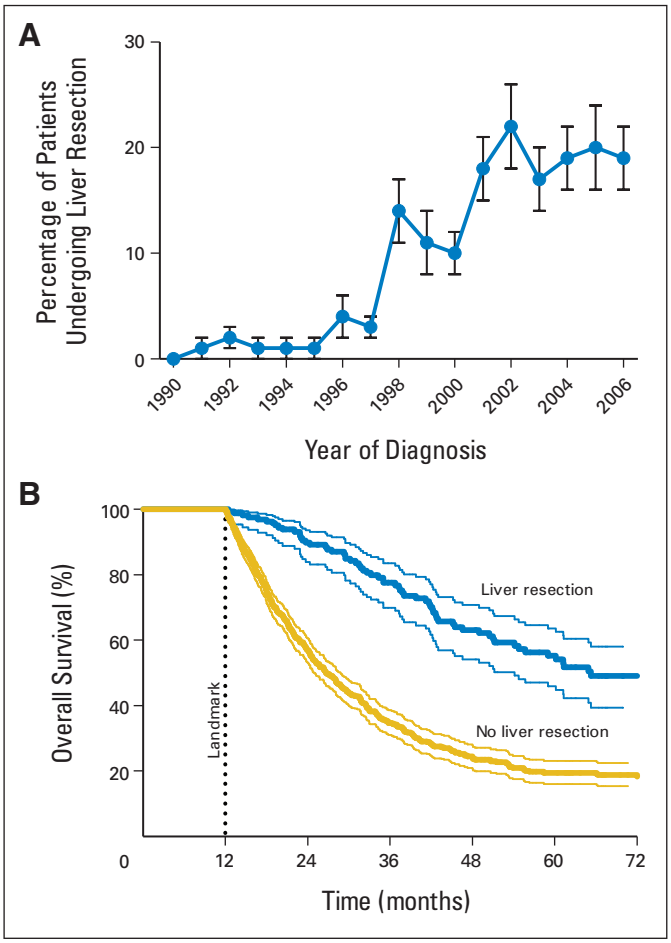

Fig 3. (A) Percentage of patients undergoing liver resection by date of diagnosis increased significantly for patients diagnosed in 1998 and stabilized around 20% for patients diagnosed in 2000 to 2006. Error bars represent SEM. (B) Overall survival by landmark analysis of patients with metastatic colorectal cancer diagnosed between 1998 and 2006 and treated at the institutions. Of those patients alive at 12 months, median overall survival was 65 months in the population of patients who underwent liver resection during the first year. Error bars represent 95% CIs.

records demonstrates a temporal association of these improvements with the adoption of additional medical treatment options beyond FU (Fig 5).

To confirm this institution-based trend in improved overall survival for a larger population, the SEER database was queried to identify survival trends since 1990. Although this database represents a different population than the institutional registries and more recent follow-up data are not yet available, similar survival trends were evident in the 49,459 patients with CRC identified. For the period from 1990 through 2003, the median overall survival time increased minimally (from 8 months to 9 months). However, for patients diagnosed in 2004 or 2005, the median overall survival time was 11 months, with an HR of 0.88 (95% CI, 0.86 to 0.89; $P < .001$) compared with 1990 through 1997 and an HR of 0.85 (95% CI, 0.82 to 0.88; $P < .001$) compared with 1998 through 2003. Although the absolute improvement was smaller than that seen in the institutional databases, the 5-year overall survival rate also significantly increased starting in 1998 (Fig 6).

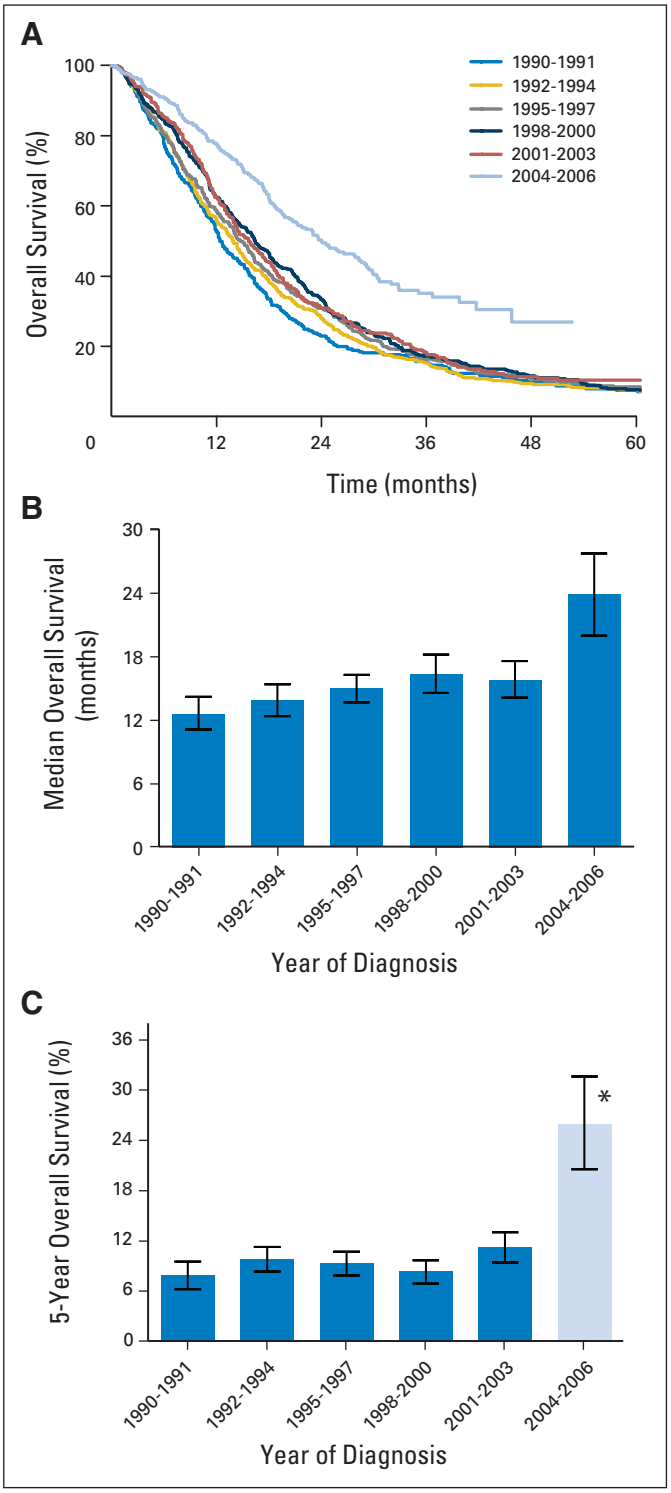

Fig 4. Overall survival for patients with metastatic colorectal cancer treated at the institutions, after censoring patients who underwent liver resection. (A) Kaplan-Meier curve. (B) Median overall survival. Error bars represent 95% CIs. For 2004 to 2006, median overall survival time was 23.9 months (95% CI, 20 to 27.8 months). (C) Five-year overall survival. Error bars represent SEM. (*) For 2004 to 2006, this represents a statistical projection of 5-year overall survival. Error bars represent 95% CI.

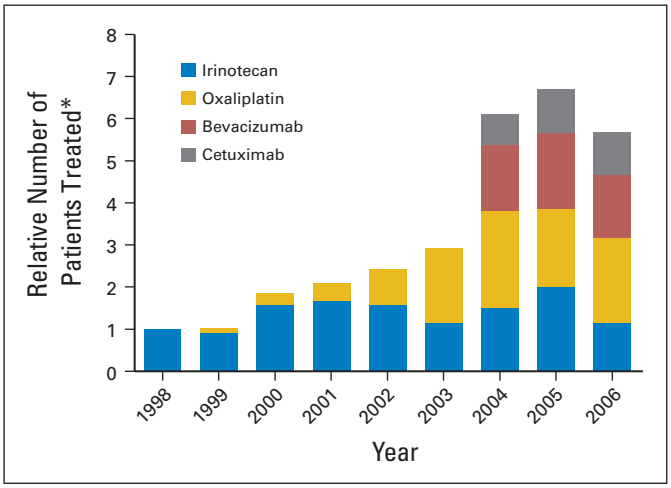

Fig 5. The use of novel chemotherapeutics increased between 1998 and 2006, with a rapid change in 2004. (*) Compared with irinotecan use in 1998 and normalized by yearly patient volume. Details of normalization under Methods.

DISCUSSION

Using institutional and US population databases, this study demonstrates a significant improvement in overall survival for patients diagnosed with metastatic CRC over the last decade. The results of our study suggest that these developments occurred in two stages at the two institutions. The first stage of improvement started with patients diagnosed in 1998 and was associated with increased utilization of hepatic resection. After an initial rapid incorporation into clinical practice, the number of patients undergoing hepatic resection has stabilized at approximately 20% of the patients with metastatic CRC in these two institutions over the last several years. In this population-based study, the rates of hepatic resection and survival after resection are comparable to outcomes reported for patients in retrospective surgical series.[13-18] Censoring of patients undergoing liver resection from the survival curves demonstrates that the hepatic surgery group is largely responsible for the improvement in 5-year survival before 2004 because there was minimal improvement in survival during this time for patients treated with medical therapy alone.

Prior reports of hepatic resection outcomes have been criticized for selection bias.[9] This is likely a valid criticism because patients are commonly referred to large centers for the purposes of hepatic resection. Our study, however, includes only patients who received primary treatment at the respective institutions, a factor that mitigates some, although not all, of the effects of referral bias by excluding patients presenting to the institutions only for hepatic resection. In support of this, the 231 patients who underwent hepatic resection in the institutional-based database only represent 11% of the total patients with CRC who underwent hepatic resection at the two institutions during this time period. Quantifying the degree of benefit from hepatic resection is also difficult in the absence of a controlled trial because retrospective studies, such as this one, fail to account for difficult-to-capture prognostic factors that introduce selection bias in favor of improved outcomes from hepatic resection.

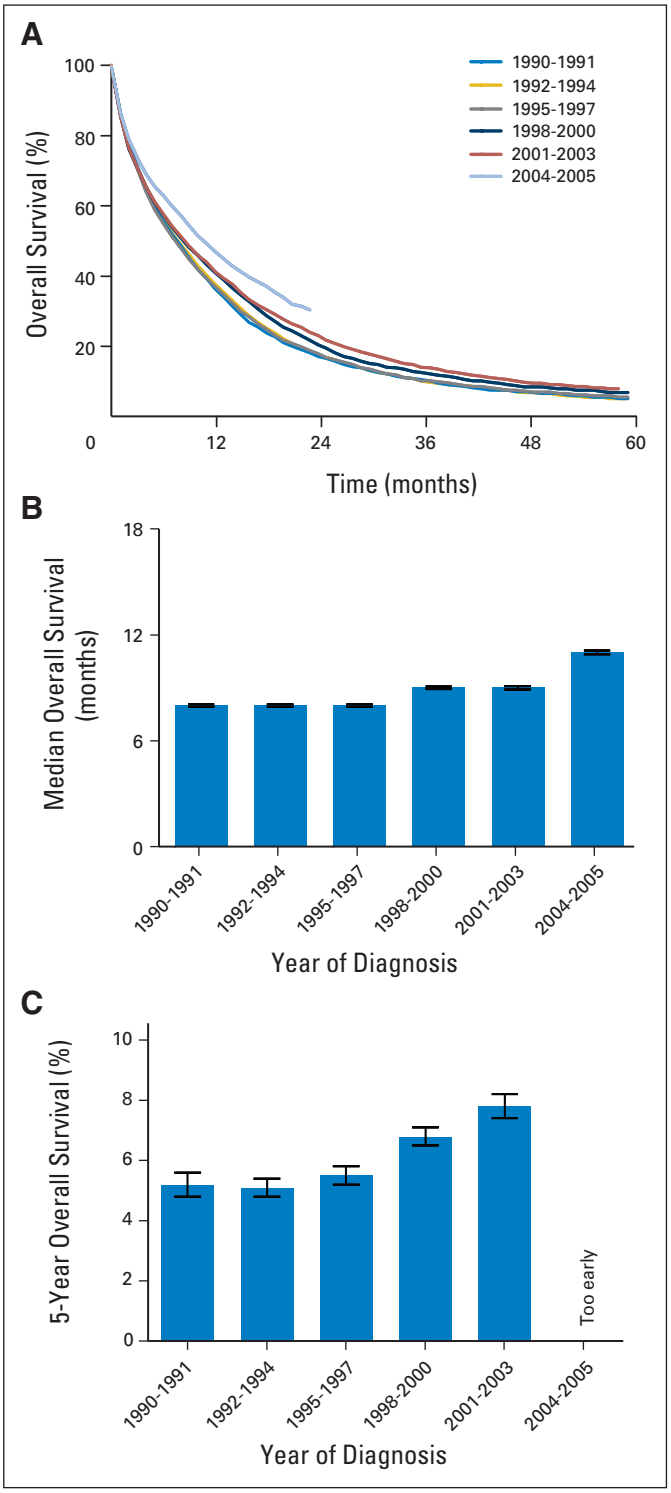

Fig 6. Overall survival for patients with metastatic colorectal cancer in the Surveillance, Epidemiology, and End Results registry. (A) Kaplan-Meier curve. (B) Median overall survival. Error bars represent SEM. (C) Five-year overall survival. Error bars represent SEM. $P < .001$ for all comparisons of later periods with 1990 to 1997.

The second stage of survival gains started in 2004 and is most likely attributable to medical therapy. Around this time, several additional drugs became available for use in the United States for treating patients with metastatic CRC, including oxaliplatin (2002),

bevacizumab (2004), and cetuximab (2004). Notably, improvements after 2004 correlate with a rapid increase in the use of these agents. This temporal trend was confirmed in our analysis of the SEER data set; however, because of the update schedule for the SEER data, these results are early, and limited follow-up is available.

The extent and rapidity of this change is uncommon for a major tumor type; however, similar events have occurred before in other cancers. For example, metastatic breast cancer has undergone considerable improvements in outcome over the last 15 years attributable to the incorporation of aromatase inhibitors and taxane chemotherapy. Specifically, in the 6-year period from 1994 to 2000, metastatic breast cancer survival rates improved dramatically, with 3-year overall survival increasing from 27% to 44% (HR, 0.63)[19]; this improvement is similar to the degree of change seen in our study of metastatic CRC (HR, 0.47 comparing overall survival before 1998 with overall survival after 2003).

The discordance in median overall survival between the population and institutional databases reflects several inherent limitations of institutional results. Although we limited our analysis of the institutional data to patients undergoing primary therapy in the academic institutions to prevent inclusion of traveling, high performance status, second-opinion patients, a referral bias likely remains.[20] In addition, these results overestimate survival times and overall survival rates by excluding patients who did not receive any treatment because of poor performance status or preference. Also, other modalities besides improved medical care and hepatic resections may have contributed to the results seen. For example, we did not separately evaluate patients undergoing surgical resection of metastatic disease at extrahepatic sites, although select patients seem to derive a benefit from resection of lung or peritoneal metastases.[21,22]

How can these findings be applied to improve metastatic CRC outcomes for the population? As is the current emphasis in medical oncology, optimization of current chemotherapy regimens and further development of novel agents will continue this progress in survival benefit. However, these results suggest that improvements in survival from liver resection preceded recent improvements from chemotherapy. Although hepatic resection lacks the publicity and advertising resources available to new pharmaceutical developments, it has significantly impacted the survival of the CRC population. For example, this study suggests that increasing hepatic resection rates from 6% to 20% of the metastatic CRC population would provide an overall population survival benefit (HR, 0.86) similar to the benefit of front-line metastatic CRC treatment derived by the addition of irinotecan to FU (HR, 0.78).[23] This finding reinforces the potential benefit of expanded incorporation of hepatic resection. Liver resection rates in older trials were quite low and have not noticeably increased in the latest phase III trials. For example, in the Intergroup N9741 study, which enrolled patients from 2001 to 2002, only 3.3% of patients underwent hepatic resection.[24] More recent phase III trials demonstrated similarly low rates of 4% to 6%.[25,26] These low rates may represent lost opportunities to improve patient outcomes through incorporation of hepatic resection.

However, there are limitations to expanding the incorporation of hepatic resection. Close coordination with medical oncologists, radiologists, and surgeons to develop a multimodality approach for each individual patient is needed to optimize outcomes. Eligibility for hepatic resection is an evolving concept and includes factors such as anticipated remnant liver volume, response to and duration of prior chemotherapy, and medical comorbidities.[7,27] Despite improvements in the surgical techniques and patient selection for hepatic resection, the number of patients eligible for this approach is unlikely to increase significantly above 25% as a result of the presence of unresectable hepatic and extrahepatic disease.

These findings suggest that the prevalence of patients alive with metastatic CRC will continue to rapidly increase as patients live longer with the disease. Indeed, according to the proportional hazards model derived from the institutional databases, we predict that more than 30% of patients diagnosed with metastatic CRC after 2004 will be alive at 5 years. This prediction, if realized, will represent a continued and significant change in the demographics of metastatic CRC. By continued advances in pharmaceutical development combined with appropriate use of liver resection, we hope that these gains may be amplified and extended to further improve patient survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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