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Patterns of Care for Adjuvant Therapy in a Random Population-Based Sample of Patients Diagnosed with Colorectal Cancer

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OBJECTIVES: Over the past decade, clinical trials have proved the efficacy of treatments for colorectal cancer (CRC). This study tracks dissemination of these treatments for patients diagnosed with stage II and III disease and compares risk of death for those who received guideline therapy to those who did not.

METHODS: We conducted a stratified randomly sampled, population-based study of CRC treatment trends in the United States. Multivariate models were used to explore patient characteristics associated with receipt of treatments. We pooled data with a previous study—patients diagnosed in 1987–1991 and 1995. Cox proportional hazards models were used to assess observed cause-specific and all-cause mortality.

RESULTS: In 2000, guideline therapy receipt decreased among stage III rectal cancer patients, but increased for stage III colon and stage II rectal cancer patients. As age increased, likelihood of receiving guideline treatment decreased ($p < 0.0001$). Overall, race/ethnicity was significantly associated with guideline therapy ($p = 0.04$). Rectal patients were less likely to have received guideline treatment. Consistent with randomized clinical trial findings, all-cause mortality was lower in patients who received guideline therapy, regardless of Charlson comorbidity score.

CONCLUSIONS: Mortality was decreased in patients receiving guideline therapy. Although, rates of guideline-concordant therapy are low in community clinical practice, they are apparently increasing. Newer treatment (oxaliplatin, capecitabine) started to disseminate in 2000. Racial disparities, present in 1995, were not detected in 2000. Age disparities remain despite no evidence of greater chemotherapy-induced toxicity in the elderly. More equitable receipt of cancer treatment to all segments of the community will help to reduce mortality.

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INTRODUCTION

Almost half of the colorectal cancer (CRC) patients who undergo surgery without adjuvant treatment risk relapse and death from metastatic disease (1). Clinical trials have demonstrated the efficacy of new treatments for CRC. It is unclear whether these therapies have sufficiently disseminated into community clinical practice to contribute to declines in mortality rates (2), or whether potential exists for improved dissemination of these therapies. We aim to evaluate recent trends in the dissemination of proven adjuvant therapies for CRC.

The NIH Consensus Conference (1990) advocated clinical use of 5-fluorouracil (5-FU) with levamisole for stage III colon cancer (3). During the 1990s, this was supplanted by 5-FU with leucovorin, based on clinical trial evidence (4–8). The 5-FU/leucovorin regimen is favored over 5-FU/levamisole as treatment is for a shorter duration, reducing patient morbidity (9, 10). Chemotherapy in patients with stage II colon cancer is controversial (11); patients have a relatively good prognosis, whereby resection alone may be curative (12). Clinical trial results remain inconclusive; NSABP trials indicated improved survival (6, 13), however, the IMPACT-B2 trial (1999) found no survival benefit at 5 yr for stage II patients treated with 5-FU/ leucovorin (12). More recent clinical trial results have indicated beneficial effects of capecitabine for stage III and 5-FU-leucovorin supplemented with oxaliplatin in the treatment of stages II and III colon cancer (1, 14–17). Irinotecan has also been assessed in combination with 5-FU/leucovorin, but no statistically significant improvement in event-free survival has been observed (18, 19). The extent of use of these compounds in routine clinical practice is not known.

Adjuvant treatment for rectal cancer includes surgery with chemoradiotherapy (5). Uncertainty surrounds the benefits of pre- *versus* postoperative radiotherapy. Decreased local recurrence has been demonstrated in patients treated with 5-FU and postoperative radiotherapy (20–22). However, recent studies report improved local control and reduced toxicity in patients treated with preoperative versus postoperative radiotherapy (23).

Despite the beneficial effects of guideline treatments within clinical trials, studies have indicated that they may be under-used in clinical practice (22, 24, 25). Research suggested that use of guideline therapy for CRC increased in the early 1990s, but varied depending on patient age, gender, and race/ethnicity (26). This population-based study aims to monitor the dissemination of guideline and clinical trial recommended treatments for CRC and to investigate the association of patient, clinical, and provider characteristics with receipt of this therapy in the United States. We further explore whether survival in our population-based cohort treated in community settings is improved for those receiving guideline therapy compared with those who do not.

METHODS

Inclusion/Exclusion Criteria

The National Cancer Institute's Surveillance Epidemiology and End Results program (SEER), covering the metropolitan areas of Atlanta, Detroit, Los Angeles, San Francisco, San Jose, and Seattle, and the states of Hawaii, New Mexico, Iowa, Connecticut, Alaska, and Utah served as the sampling frame for these patients. Patients, aged at least 20 yr, newly diagnosed in 2000 with histologically confirmed stage II and III CRC, were eligible for inclusion. Patients were excluded if diagnosis was at autopsy, death certificate, if this was a second malignancy, other than nonmelanoma skin, or they were simultaneously diagnosed with another cancer. Individuals were sampled by cancer site and gender, with oversampling of African-Americans and Hispanics. A total of 878 cases were sampled in 2000. Hawaii and Alaska participated in a single year of the studies. Their 19 cases plus 32 cases with no cancer-directed surgery were excluded from further analyses, leaving 827 cases. We pooled our data with that of a previous study of stage II and III CRC diagnosed in 1990, 1991, and 1995, as per Potosky *et al*., 2000 (26). Identical inclusion and exclusion criteria were used in all years.

Data Collection

This was an NCI-sponsored patterns of care (POC) study. The NCI-sponsored POC data collection involved the reabstraction of hospital medical records by SEER abstractors to verify information on patient demographics, tumor characteristics, and treatment planned or given within 4 months of diagnosis. All listed comorbid conditions were recorded and coded by a single Registered Health Information Technologist. Comorbidity scores were based on conditions present at the time of diagnosis with CRC, using the Charlson index (27). Because patients often receive treatment outside the hospital setting and chemo- and hormonal therapy are known to be underreported in hospital records, each patient's treating physician was contacted to verify therapy provided. The names of specific agents given, but not dose or duration, were recorded.

Tumors were defined according to AJCC staging, stage II: T3 or T4 with no positive regional lymph nodes, and stage III tumors: T1 to T4 with positive regional lymph nodes. Grade was collected from pathology reports. The highest grade was recorded. Age, gender, race/ethnicity, and marital status were abstracted from the hospital medical record. Race/ethnicity was categorized as non Hispanic white, nonHispanic black, Hispanic, and all other races. Marital status was categorized as married and all other (single, divorced, widowed, or unknown). Income was not available from the hospital records. Therefore, we used the patient's census tract at the time of diagnosis to link to the U.S. Census data. We obtain information on median family income for the census tract in which the patient resided and applied this to the patient. The number of nodes examined and number of positive nodes were recorded as reported in the pathology report. The registries participating in this study maintain an active follow-up of all patients and vital status is reported at the end of each year. We used these data to examine survival.

Treatment

We considered guideline concordant therapy for stage III colon cancer as adjuvant 5-FU plus leucovorin. Although there were no patients who received 5-FU plus levamisole in 2000, we categorized the 22% of patients who received 5-FU plus levamisole in 1991 as having received guideline therapy. We documented the most commonly used cancer drugs (*e.g.,* capecitabine, irinotecan, oxaliplatin). Because of low numbers of patients, we did not assess the use of these drugs in our multivariate analyses. For stage II colon cancer, given the lack of consensus regarding a minimal standard of care, we did not include these patients in our regression or survival analyses; however, they are included in selected tables for completeness of reporting. For rectal cancer, guideline therapy was defined as 5-FU with radiotherapy. We classified patients who were offered and refused cancer-directed treatment with those having received treatment.

The graphs that track trends in guideline therapy using data from 1987 to 1991, 1995, and 2000 and include only registries that participated in all study years to minimize any geographic variation in treatment by year because of inclusion of registries in some years and not others. A total of 5,601 cases were included. One case was excluded because of unknown stage, 33 (0.6%) cases had no surgery and 1,005 (13%) cases were excluded from Los Angeles, San Jose, and Utah because these registries did not participate in all years of the study.

Statistical Analyses

Data analyses were performed using the statistical packages Stata 8.0 and SUDAAN (Research Triangle Institute, Research Triangle Park, NC) for multivariate regression

Table 1. Distribution of Clinical and Nonclinical Characteristics for Colorectal Cancer Patients 2000 Patterns of Care study (N = 827)

	Colon Stage II N = 212	Weighted (%)	Colon Stage III N = 263	Weighted (%)	Rectal Stage II N = 127	Weighted (%)	Rectal Stage III N = 225	Weighted (%)
Age								
<55	30	9.1	57	16.6	21	12.3	67	22.7
55–64	50	22.4	50	16.8	26	25.7	51	24.1
65–74	63	33.0	66	21.7	47	35.9	57	26.7
75–79	23	12.6	35	15.8	16	9.1	23	10.9
80+	46	22.9	55	29.2	17	17.1	27	15.6
Sex								
Men	109	52.2	131	43.7	67	49.8	109	49.8
Women	103	47.9	132	56.3	60	50.2	116	50.2
Race								
White nonHispanic	76	73.1	92	74.5	62	80.7	89	73.7
Black nonHispanic	50	9.0	66	9.9	23	7.2	45	9.1
Hispanic	48	8.8	45	6.7	21	5.9	42	8.4
Other	38	9.1	59	8.8	21	6.2	49	8.8
Unknown	0	0	1	0.1	0	0	0	0
Marital status								
Married	110	57.4	152	55.2	75	61.4	124	54.1
Other	102	42.6	111	44.8	52	38.6	101	45.9
Tumor extent								
T1–T2	0	0	30	13.6	0	0	31	12.8
T3	156	75.7	181	62.2	99	81.8	162	74.2
T4	56	24.4	52	24.3	28	18.2	29	10.6
Unknown	0	0	0	0	0	0	3	2.4
No. of positive nodes								
None	210	99.4	0	0	115	89.0	0	0
1–3 nodes	0	0	171	63.5	0	0	141	67.4
≥4 nodes	0	0	84	33.6	0	0	73	28.4
Positive but # unknown	0	0	8	2.9	0	0	8	3.7
Unknown or not stated	2	0.7	0	0	12	11.0	3	0.6
Differentiation grade								
Well/moderately differentiated	159	72.3	185	68.3	104	83.7	160	72.4
Poorly differentiated/undifferentiated	46	24.1	70	29.4	20	14.9	58	25.4
Unknown	7	3.6	8	2.3	3	1.5	7	2.1
Charlson score								
One+	50	25.66	66	21.7	34	23.3	43	22.7
None	162	74.3	197	78.3	93	76.7	182	77.3
Cause of death								
Alive	161	76.6	184	68.9	96	76.0	161	72.8
Colorectal cancer	24	9.1	55	23.2	22	16.7	48	18.5
Other cause of death	27	14.3	24	7.9	9	7.3	16	8.7

Weighted by the sampling fraction.

analyses. Data were weighted to the SEER population from which cases were drawn. Univariable analyses were carried out using 2-tailed χ^2 tests and p-values (significant at <0.05) to evaluate therapy receipt for each cancer site and stage, with demographic and clinical categorical variables. Multivariable analyses were conducted using logistic regression. We present observed and adjusted percentages of patients receiving guideline treatment and in the receipt of 5-FU-based treatment in addition to odds ratios. Adjusted percentages were obtained from the estimates of the probability for each individual receiving treatment in the logistic regression models. These percentages were directly standardized to the distribution of the covariates among the entire weighted sample (28). Differences in the proportions of patients who received each treatment for a particular year (1995–2000) were assessed using a Z-test.

We used Cox Proportional Hazards Regression models to analyze all-cause and cancer-specific mortality, combining data from a previous POC study (26) including the years 1990, 1991, 1995 with 2000. We only included cases beginning in 1990 to coincide with collection of comorbid conditions. Cases from all registries participating in any year are included in the survival analyses. For the earliest years, a maximum 12-yr follow-up period was complete through December 2002. The Wald F-test was used to test hypotheses about interactions using methods similar to those used to test hypotheses on main effects. The log-rank test and likelihood ratio tests were used to assess validity of the models.

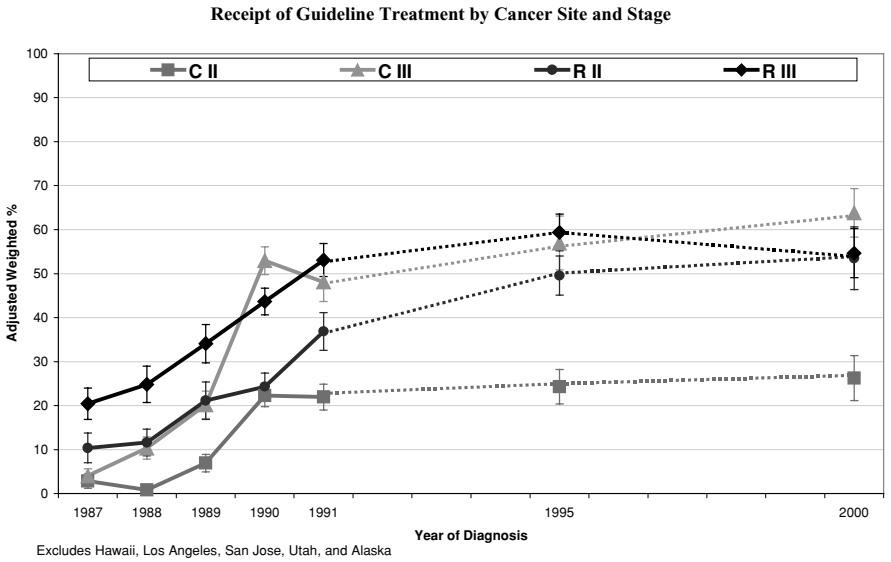


Figure 1. Adjuvant therapy (colon: 5-FU and levamisole or leucovorin) (rectal: 5-FU and radiation) offered or received by patients. All percentages are weighted for the sample fraction. Treatment by site and stage for colorectal cancer.

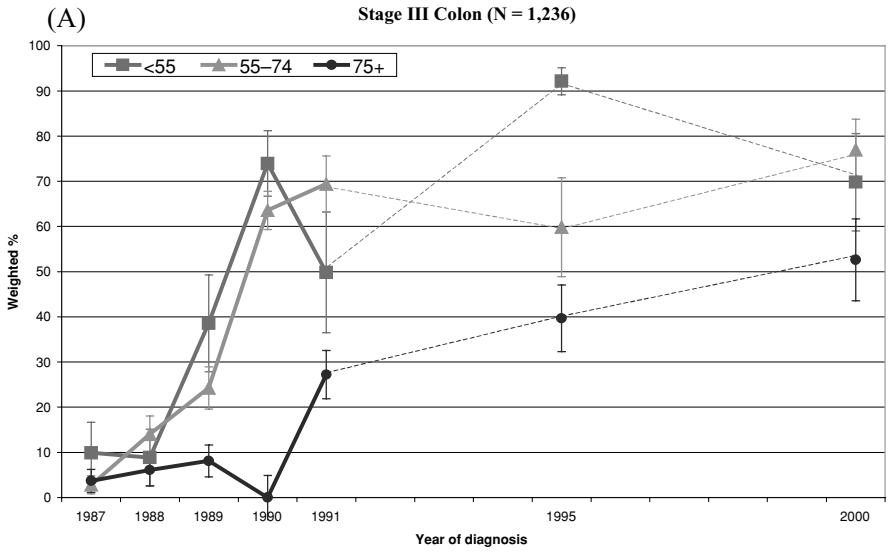
RESULTS

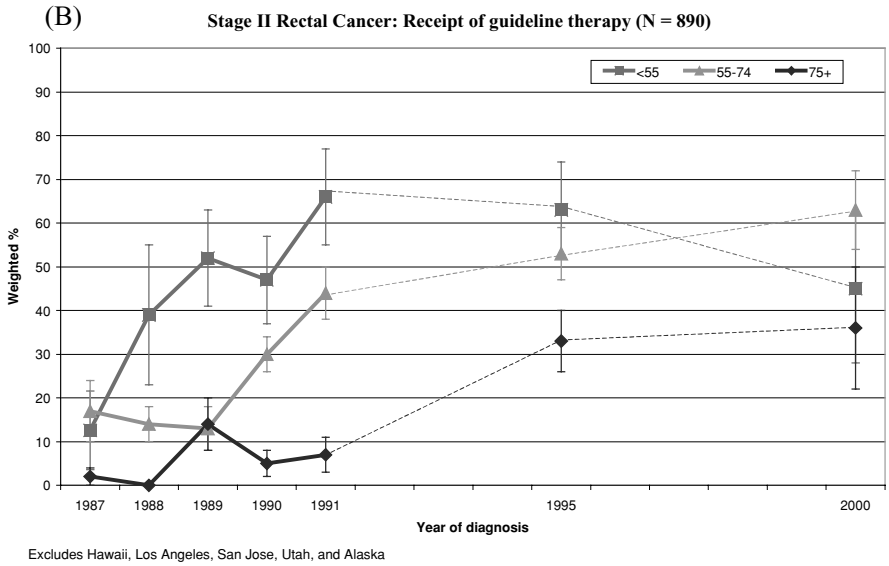
Table 1 illustrates the demographic and clinical characteristics of cases diagnosed in 2000 by cancer site and stage, with weighted percentages and the unweighted number of patients sampled. Figure 1 illustrates guideline therapy receipt by site and stage and includes data from registries that participated in all years of the studies. There was a slight decrease in the proportion of stage III rectal patients who received guideline therapy. Prevalence of guideline therapy increased somewhat from 1995 to 2000 for all other stage and site groups.

Figure 2 tracks guideline treatment receipt by age among patients with stage III colon, stage II, and stage III rectal cancer. For stage III colon cancer (Fig. 2A), in 1995 there was a significant decrease in the percentage receiving guideline treatment as age group increased. In 2000, there was a decrease in the percentage receiving guideline therapy for those aged <55 yr from 92% (95% CI 84–96%) in 1995 to 70% (95% CI 46–86%) in 2000, and an increase among patients aged 55–64 from 60% (95% CI 38–78%) to 77% (95% CI 61–88%) and ≥75 yr from 40% (95% CI 26–55%) to 52% (95% CI 35–69%). From 1995 to 2000 there were also nonsignificant changes in the receipt of guideline treatment; with a decrease in patients with stage II rectal cancer aged <55 yr, a slight increase in those aged 55–74 yr, and little change for patients aged ≥75 yr (Fig. 2B). Although not statistically significant, the receipt of guideline treatment decreased for stage III rectal patients (Fig. 2C) aged ≤75 yr in 2000 compared with 1995 and increased slightly for patients aged 75 and older. There was little variation in receipt of specific types of therapies for rectal cancer between 1995 and 2000, radiation only, 5 F-U only, or 5 F-U-radiation combined (not shown). Like previous years, the unadjusted proportion of patients who received any of these therapies was higher in stage III than stage II rectal cancer patients. Figure 3 tracks the prevalence of preoperative *versus* postoperative radiation for rectal cancer patients, and indicates increased receipt of preoperative, 5% (95% CI 3–9%), to 14% (95% CI 9–21%), with corresponding decreased postoperative radiation, 53% (95% CI 47–59%) to 43% (95% CI 34–52%).

Table 2 outlines treatment receipt by cancer site and stage. Overall, 59% of patients received 5-FU-based chemotherapy, 50% received guideline therapy. Sixty-one percent of stage III colon cancer patients received 5-FU combined with leucovorin or levamisole (FL) (guideline). For stage III colon cancer patients, most who received oxaliplatin, irinotecan, or capecitabine also received the FL regime, 0.1% (N = 1) received oxaliplatin without FL, 0.4% (N = 2) received irinotecan without FL, and 0.5% (N = 2) of stage III colon cancer patients received capecitabine without FL. Thus, a total of 5 stage III colon cancer patients, who received these drugs without FL, were categorized as having not received guideline therapy. The proportion of patients who received 5-FU-based chemotherapy is higher than "guideline" for rectal, as some cases did not receive radiotherapy, and for colon, as some cases did not receive leucovorin/levamisole after 5-FU. Patients who received 5-FU but did not receive radiotherapy amounted to 6% of all stage II and 15% of all stage III rectal cancer patients.

Sociodemographic and clinical factors were analyzed using multivariable regression to test their association with the receipt of 5-FU-based chemotherapy (not presented) and, in a separate model, guideline therapy (Table 3) for patients diagnosed in 2000 with stage III colon cancer and stage II and III rectal cancer. The models were similar; however, the magnitude of the association of age with the receipt of treatment was far greater among patients in the 5-FU-based chemotherapy model (OR = 13.5 for those aged <55 yr)





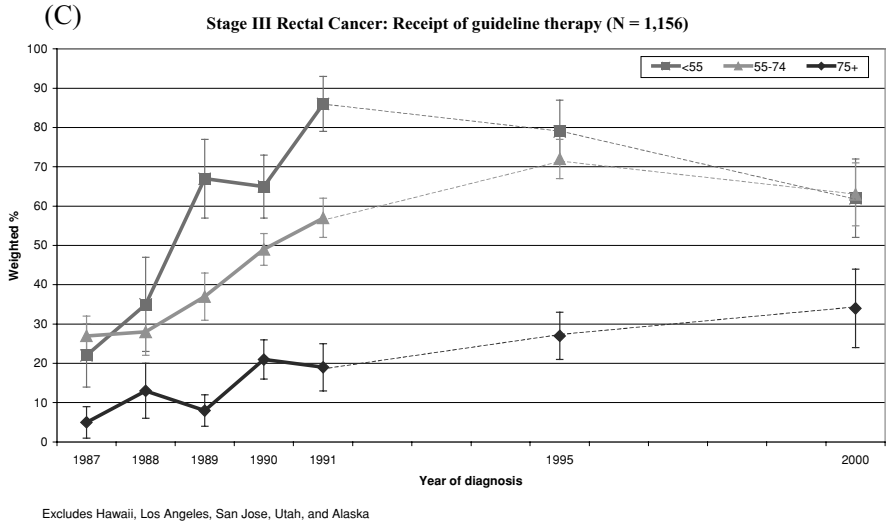


Figure 2. Adjuvant therapy offered or received by colorectal cancer patients by age at diagnosis. All percentages are weighted for the sample fraction. (*A*) stage III colon, (*B*) stage II rectal, (*C*) stage III rectal cancer.

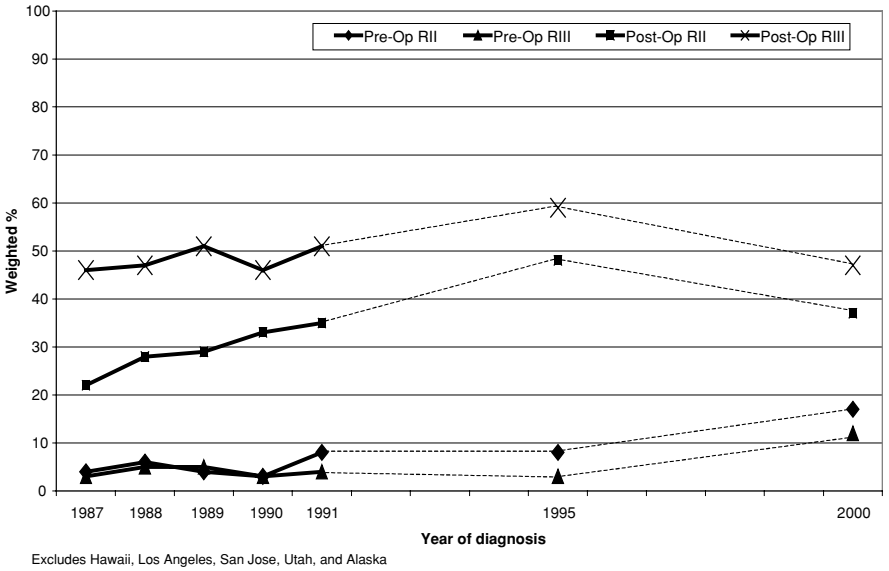


Figure 3. Pre- *versus* postoperative radiation therapy offered or received by rectal cancer patients. All percentages are weighted for the sample fraction.

than among those in the guideline therapy model (OR = 9.6 among those aged <55 yr). Younger patients were more likely to have received guideline treatment, after adjustment for all characteristics in the logistic regression models ($p < 0.0001$). Overall, race/ethnicity was significantly associated with receipt of guideline therapy ($p = 0.04$). NonHispanic blacks appeared to have received treatment more often than Hispanics or those of other and unknown races and less often than nonHispanic whites; however, these differences were not statistically significant. Overall, cancer site and stage was not associated with receipt of guideline therapy ($p = 0.06$). Stage III rectal cancer patients were less likely to have received guideline therapy (5-FU + radiation) (OR = 0.6, 95% CI 0.4–0.95). We examined, but did not find, interactions in our models among various demographic and clinical factors.

To assess whether observed survival in our cohort was consistent with that observed in randomized controlled trials (RCTs) of therapy, we analyzed mortality risk ratios (cancer-specific and all-cause) for patients diagnosed with stage III colon and stage II and III rectal cancer (Table 4). We created two separate cohorts of patients for this analysis. The first included only patients with a Charlson score of zero and the second patients with a Charlson score of one or more. In all models we included the same independent variables. For patients with a Charlson score of 0, after adjusting for age, gender, race/ethnicity, marital status, median income, cancer

Table 2. Distribution (Weighted for the Sampling Fraction) of Guideline and Emerging Guideline Treatments for Colorectal Cancer Patients 2000 Patterns of Care Study

	Total N = 827	Weighted (%)	Colon Stage II N = 212	Weighted (%)	Colon Stage III N = 263	Weighted (%)	Rectal Stage II N = 127	Weighted (%)	Rectal Stage III N = 225	Weighted (%)
Guideline*										
No	432	50.1	149	74.0	119	38.7	58	44.6	106	46.6
Yes	395	49.9	63	26.0	144	61.3	69	55.4	119	53.4
5-FU-based chemo										
No	344	40.4	139	68.0	102	34.5	43	36.8	60	26.2
Yes	483	59.3	73	32.0	161	65.5	84	63.2	165	73.8
Oxaliplatin	5	0.8	2	0.8	3	1.8	0		0	
Irinotecan	18	2.3	5	1.6	8	4.6	0		5	1.5
Capecitabine	9	1.0	2	1.5	2	0.5	2	0.8	3	1.1
Clinical trial										
No	803	95.6	206	96.5	254	93.7	125	97.6	218	96.2
Yes†	24	4.4	6	3.5	9	6.3	2	2.4	7	3.8

*Guideline = 5-FU + leucovorin/levamisole for colon III (FL), 5-FU + RT for rectal II & III.
†This category includes patients who were recommended or refused entry into a clinical trial.

Table 3. Association of Use of Guideline Therapy: 5-FU + Leucovorin/Levamisole (Colon Stage III) and 5-FU + RT (Rectal Cancer) with Clinical and Nonclinical Characteristics for Patients Diagnosed with Colon Cancer Stage III and Rectal Cancer Stage II & III (N = 615) in 2000

Characteristic	*p*-Value	Observed % (Weighted)	Adjusted % (Weighted)	Adjusted OR	95% CI
Age at diagnosis	<0.0001				
80+ (REF)		30	25	1.0	
75–79		57	59	5.3	2.3–12.3
65–74		63	65	7.4	3.6–15.1
55–64		69	68	8.3	3.8–18.2
<55		67	70	9.6	4.3–21.4
Race	0.04				
Black nonHispanic (REF)		53	56	1.0	
White nonHispanic		59	60	1.2	0.6–2.3
Other		50	47	0.7	0.4–1.3
Cancer site & stage	0.06				
Colon III (REF)		61	64	1.0	
Rectal II		55	52	0.6	0.3–1.0
Rectal III		53	53	0.6	0.4–0.95

Model also adjusted for registry, Charlson score, grade, marital status, median income and gender.

stage, tumor grade, year of diagnosis, and registry, the use of guideline therapy was associated with a decreased hazard ratio for all cause mortality (HR = 0.70, 95% CI 0.57–0.86), but did not reach statistical significance for cause-specific deaths (HR = 0.80, 95% CI 0.63–1.02). Only grade of the tumor and median income were associated with cause-specific mortality. The second set of models included patients with a Charlson score of one or greater and indicated that again, the use of guideline therapy was associated with lower all cause mortality (HR = 0.54, 95% CI 0.40–0.71). However, in these patients with a Charlson score of one or greater, the use of guideline therapy was also associated with decreased cause-specific mortality (HR = 0.56, 95% CI 0.38–0.85). NonHispanic whites with Charlson scores of zero had significantly lower all-cause mortality (HR = 0.74, 95% CI 0.58–0.94) compared with nonHispanic blacks, but there was no other significant racial difference in mortality.

DISCUSSION

Patients with stages II and III disease represent the majority of CRC patients (26, 29–34). This population-based study monitored treatment trends, analyzed factors associated with guideline therapy receipt, monitored the dissemination of newer treatments into community clinical practice, and assessed the effects of such treatment on population-based observed survival in patients diagnosed with stages II and III CRC.

Studies have found differential treatment for patients within the same disease stage (6, 13, 35). Treatment variability among patients in our study may be attributable to differences in subgroups at presentation, *e.g.,* larger tumors in one subgroup despite similar stage. Treatment selection may have been based on a preference to forego the toxicity of adjuvant chemotherapy (although refusals were coded as having received guideline therapy), in addition to avoid aggravating any underlying comorbid conditions, particularly among older patients (9, 13). In the graphs, we did not adjust for the prognostic factors included in logistic regression models, so our graphs do not account for patient factors that may have contributed to treatment trends.

Oxaliplatin has recently been recommended for the treatment of stage III colon cancer as part of the FOLFOX combination regime (*i.e.,* combined with 5-FU and leucovorin) (1, 14, 17). In our analyses, 8.7% of patients received oxaliplatin combined with 5-FU/leucovorin. Although the application for approval of oxaliplatin was presented in March 2000, approval was not granted until August 14, 2002 (http://www.fda.gov/cder/drug/infopage/eloxatin/default.htm). However, patients who received 5-FU/leucovorin/levamisole with oxaliplatin were classified as having received guideline therapy. The same is true for those patients who received irinotecan (4.2%) as part of the FOLFIRI regime (5-FU/leucovorin/irinotecan). The X-ACT trial assessed the benefit of capecitabine compared with 5-FU/leucovorin for stage III colon cancer. The results of this trial have

Table 4. Adjusted Cox Proportional Hazards Models for Death from all Causes and Death from Colorectal Cancer by Charlson Score

	Charlson Score = 0		Charlson Score > 0	
	All-cause	Cause-specific	All-cause	Cause-specific
	OR (LL, UL)	OR (LL, UL)	OR (LL, UL)	OR (LL, UL)
Guideline therapy*	0.7 (0.6, 0.9)	0.8 (0.6, 1.02)	0.5 (0.4, 0.7)	0.6 (0.4, 0.9)

*Adjusted for age, gender, race/ethnicity, marital status, median income, cancer site, stage, grade, year of diagnosis, and registry.

indicated that the regimens have equitable efficacy but that capecitabine had a similar toxicity profile in older as in younger patients (15, 16). In our analyses, patients who received capecitabine *in lieu* of 5-FU and leucovorin were categorized as not receiving guideline treatment (N = 2), thus, the effects of excluding them from our logistic regression models are likely negligible. Although the benefit of irinotecan, oxaliplatin, and capecitabine was still being assessed at the time of diagnosis of these patients and they were not recommended in consensus guidelines, our study indicates that these novel therapies were available in 2000 to some eligible patients outside clinical trials.

RCTs have indicated the benefit of adjuvant therapy for stage III colon cancer (11, 13, 15–17). The increase from 1995 to 2000 in the percentage of stage III colon cancer patients aged over 55 yr who received treatment (presented in the graphs) may reflect an increased understanding among patients of the benefits of chemotherapy. We observed a nonsignificant decrease in the proportion of patients aged less than 55 who received 5-FU and leucovorin. Three of these patients received oxaliplatin, irinotecan, or capecitabine without the 5-FU/leucovorin/levamisole regimen. Therefore, it is unlikely that the apparent decrease in the receipt of treatment from 1995 to 2000 is attributable to treatment with one of the above alternative drugs *in lieu* of guideline treatment.

The NSABP R-02 trial results (2000) indicated fluorouracil-based chemotherapy improved survival, while postoperative radiotherapy with chemotherapy reduced local recurrence rates when compared with chemotherapy alone in rectal cancer (36). Stage II rectal cancer has a high survival rate and low recurrence risk (37). A preference to avoid side effects, including sphincter destruction, loss of pelvic control, etc., may account for our findings of decreased treatment among patients aged less than 55 yr. A study by Gunderson *et al.* (38) considered surgery, radiation, plus chemotherapy excessive for patients with only intermediate risk (*i.e.,* T1-2/N1, T3/N0) tumors. Another study indicated that radiation therapy for rectal cancer can induce more toxicity in elderly patients than their younger counterparts (20); however, we observed slight increases in the receipt of chemotherapy and radiation among patients aged over 75 yr.

Recently, Sauer *et al.,* demonstrated improved locoregional disease control and reduced treatment toxicity in patients who received preoperative *versus* postoperative chemoradiotherapy (23). In addition, Kapiteijn *et al.* indicated reduced local recurrence with preoperative radiotherapy (20). In Europe and the United States, there is a shift toward administration of preoperative chemoradiotherapy for rectal cancer (39). Our findings in this community-based setting provide evidence of a corresponding increase in preoperative *in lieu* of postoperative radiation.

The inverse association between age and neo/adjuvant treatment observed in our study has been widely documented (40–42). A study by Sargent and colleagues indicated that selected elderly patients could benefit comparably to their younger counterparts from cancer-directed treatment (41). Research has reported reduced chemotherapeutic doses in elderly patients (43). Studies have indicated that the elderly are reluctant to trade quality of life for prolonged survival (40, 44), noting that older patients are more likely to reject treatment when offered it (31, 34). We accounted for this, through classifying patients who were offered and refused treatment as having received guideline therapy. However, it is possible that some physicians did not indicate "refusal" for older patients in which there was mutual agreement that adjuvant therapy did not provide sufficient benefit.

Studies have reported racial disparities in the receipt of cancer-directed treatment (26, 45, 46). African-Americans have the highest incidence and lowest survival rates of CRC (47–50), frequently presenting with more advanced disease than their white counterparts (51, 52). Although we observed an overall significant trend between race/ethnicity and the receipt of guideline treatment, no group proved significantly more or less likely to have received the 5-FU/leucovorin treatment regimen. The earlier report (26) indicated that white patients were more likely to receive treatment. Our findings may reflect the longer interval since the initial widespread acceptance of adjuvant therapy for CRC beginning in 1990 and thus increased dissemination to minority groups (3). Additionally, campaigns by the Committee on Minority Affairs and Cultural Diversity (American College of Gastroenterology) may have increased cancer awareness among the medically underserved.

Previous findings (26) intimated that underlying health conditions contributed to a nonsignificant association between treatment receipt and all-cause, but not cause-specific, mortality. Therefore, we analyzed patients with a Charlson score of zero separately from those with scores of one or greater. Although we found survival differences for patients receiving guideline therapy, such differences must be interpreted with care because of the possible selection bias. Patients who were healthier at diagnosis and more likely to have better outcomes independent of therapy receipt may also have been more likely to receive adjuvant therapy following surgery because of their better baseline health status. Thus, differences in survival may be attributable to better baseline health, rather than to guideline therapy. Furthermore, our measure of comorbidity may yield some misclassification. The Charlson score does not distinguish between patients with identical Charlson scores who are heterogeneous in the severity of their comorbid condition, *e.g.,* a patient with severe chronic pulmonary disease has the same Charlson score as that of a patient with diabetes (Charlson score = 1).

NCI POC studies make it possible to monitor factors associated with the receipt of adjuvant therapy, treatment trends, and survival. The standardized data collection protocol used for all years enabled a nonbiased comparison. Limitations include: (1) no information on a patient's compliance to, duration of, and dose of therapy, (2) no information on surgery quality and quality of life, which may have impacted on treatment receipt, (3) limited follow-up for patients diagnosed

in 2000. Future work will include more years of diagnosis, further track newer adjuvant therapies (*e.g.,* FOLFOX, bevacizumab, etc.) not widely used in 2000, and provide longer follow-up to analyze the effects of treatment receipt on survival.

The rates of guideline-concordant therapy are low in routine practice but our findings indicate that they are increasing. The risk of all-cause mortality in both patients with a Charlson score of zero and those with a score of one or greater was significantly lower in patients who received guideline therapy. The risk of death from CRC was also lower, but in patients with a Charlson Score of zero it did not quite reach statistical significance. We did not detect racial disparities, present in our previous study; however, age disparities remain. The reduced receipt of treatment and survival among elderly patients remains a public health concern. Such patients have a reasonable life expectancy and appear to enjoy benefits equivalent to younger patients when they receive appropriate treatment. Despite the continuous emergence of newer and more effective treatments, if treatment disparities continue to disfavor the elderly, poor outcomes can be expected to worsen as the population ages. Moreover, improved dissemination of treatment to all segments of the patient community is likely to improve morbidity, mortality, and survival for CRC.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- Randomized clinical trials have demonstrated the efficacy of anti-cancer treatments for colorectal cancer, indicating improved 5-year survival rates.
- The extent of use of these treatments in routine clinical practice is not clear.
- Research has indicated less treatment of elderly and minority race/ethnicity patients.

What Is New Here

- We document the use of anti-cancer treatment for stage II and III colorectal cancer before, during and after the publication of major clinical trials.
- We report routine clinical practice use of established guideline concordant therapies, and newer, more recently investigated therapies.
- Use of guideline therapy was associated with a decreased risk of death.
- Although we found no substantial differences in treatment receipt, there were some differences in survival by race/ethnicity.
- We report age disparities in treatment receipt and survival.
- These disparities are likely to worsen as the population ages.

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CONFLICT OF INTEREST

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