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ARTICLE

Patterns of Colorectal Cancer Care in the United States: 1990–2010

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Abstract

Background: Colorectal cancer (CRC) mortality has declined in the United States, in part because of advances in treatment. Few studies have evaluated the adoption of therapies and temporal changes in patterns of care.

Methods: Patients age 20 years and older diagnosed with stages II/III CRC were randomly sampled from the population-based Surveillance, Epidemiology, and End Results (SEER) program in 1990–1991, 1995, 2000, 2005, and 2010 (n = 7057). Therapy was obtained from medical records and physician verification. We described the receipt of chemotherapy and radiation therapy. Log-binomial regression was used to examine factors associated with therapy. All statistical tests were two-sided.

Results: Chemotherapy receipt among colon cancer patients increased from 1990 (stage II: 22.5%; stage III: 56.3%) to 2005 (stage II: 32.1%; stage III: 72.4%) and declined slightly in 2010 (stage II: 29.3%; stage III: 66.4%). Stage III colon cancer patients who were older (vs <55 years, 75–79 years: risk ratio [RR] 0.81, 95% confidence interval [CI] = 0.71 to 0.91; ≥80 years: RR = 0.37, 95% CI = 0.28 to 0.47) or had a comorbidity score of 2 or higher (vs 0, RR = 0.56, 95% CI = 0.35 to 0.87) received chemotherapy less often. Receipt of radiation therapy by rectal cancer patients increased across all years from 45.5% to 66.1%. Increasing age (vs <55 years, 75–79 years: RR = 0.59, 95% CI = 0.47 to 0.74; ≥80 years: RR = 0.33, 95% CI = 0.25 to 0.45) was associated with lower chemoradiation use among stage II/III rectal cancer patients.

Conclusion: Our findings demonstrate increased adoption of chemotherapy and radiation therapy for colon and rectal cancer patients and differences in therapy by age, comorbidity, and diagnosis year. Increased receipt of these therapies in the community may further reduce CRC mortality.

The incidence and mortality of colorectal cancer (CRC) have continually declined in the United States over the past two decades. During the years 2001 to 2010, average annual mortality rates were 19.6 and 13.9 per 100 000 men and women, respectively. Mortality rates have decreased by 3.0% per year in both men and women, and the overall five-year relative survival rate has increased from 49.8% in 1975–1977 to 66.1% in 2003–2009 (1). Much of the mortality decline has been attributed to screening and advances in treatment (2).

Adjuvant chemotherapy has gained attention as a critical advance in the treatment of colon cancer. Growing evidence suggests several adjuvant chemotherapy regimens markedly improve the overall and disease-free survival of patients with resectable stage III disease (3–8). In contrast, the use of adjuvant therapy for patients with stage II colon cancer remains controversial. Clinical trial results are inconclusive, and many studies show no survival benefit for adjuvant chemotherapy over surgery alone in stage II patients (9).

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The use of preoperative radiation therapy has similarly been recognized as an important advance in the evolution of treatment for locally advanced rectal cancer (stages II and III) (10). Early randomized trials showed the benefit of postoperative radiation in decreasing local recurrence (11,12), but later trials suggested that preoperative radiation therapy also decreases the risk of local recurrence compared with surgery alone (13,14). Although overall survival is similar between patients treated with preoperative and postoperative radiation, preoperative radiation is associated with greater improvements in local control, increased rates of sphincter preservation during surgery, and fewer treatment-induced toxicities (15–17). The addition of chemotherapy to preoperative radiation (ie, chemoradiation) has since been shown to further improve local control and enhance pathological response (18–20).

Few studies have examined the adoption of recommended therapies in community settings as evidence from clinical trials has changed. We aimed to describe receipt of adjuvant chemotherapy among patients diagnosed with stages II and III colon cancer and preoperative and/or postoperative radiation therapy among patients diagnosed with stages II and III rectal cancer. We also assessed the association of receipt of therapy with patient demographic and tumor characteristics.

Methods

Participants and Procedures

Patients were sampled from the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) program. SEER routinely collects information from hospitals, pathology laboratories, surgical centers, and radiation facilities on patient demographics and tumor characteristics. Preoperative (neoadjuvant) and postoperative (adjuvant) therapies are often underreported in SEER; therefore, the NCI annually conducts patterns of care (POC) studies on a sample of patients with select cancers to assess the extent to which chemotherapy and radiation therapy are received in clinical practice (21,22).

Stages II and III CRC patients in participating SEER registries were eligible for POC studies in 1990–1991, 1995, 2000, 2005, and 2010. Eligible patients were stratified within registries by tumor site (colon or rectum), and a random sample was taken from within each stratum. Beginning in 1995, there was oversampling by race/ethnicity to obtain more stable estimates for these subgroups. Patients were sampled according to the staging scheme used by SEER in each study year. In 1990 or 1991, 1995, and 2000, patients were sampled based on Extent of Disease (EOD) 10 coding, and in 2005 and 2010 patients were sampled based on Collaborative Staging (CS) coding. EOD and CS coding record the farthest extent of disease based on the combined clinical and pathological assessment. Clinical information takes priority when a patient is treated with preoperative therapy; otherwise, pathological information takes priority. TNM staging was derived by mapping T and N status from EOD and CS coding. Stage II included T3 or T4 tumors with no positive regional lymph nodes, and stage III included any T1 to T4 tumors with regional lymph node involvement. These stage definitions also correspond approximately to stage B2 and C of the Aster-Coller modification of Duke's original staging system.

Patients were ineligible if they were younger than age 20 years, previously diagnosed with cancer (excluding nonmelanoma skin cancer), diagnosed at autopsy or on death certificate only, or diagnosed with a synchronous cancer. Patients with tumors in the appendix (n = 4) or who did not undergo cancer-directed surgery (n = 171) were further excluded.

Patients' medical records were abstracted for treatment information, including receipt of specific chemotherapy agents, radiation therapy, and dates of treatment following diagnosis. Because chemotherapy and radiation therapy are often given outside of the hospital setting and SEER data is primarily hospital-based, the treating physician was contacted to verify therapy received or recommended. Treating physicians were also asked to provide names and addresses of other physicians who may have treated the patient, who were subsequently contacted for treatment information. Doctor verification substantially improves completeness of chemotherapy ascertainment or confirms that no chemotherapy or radiation was given. Physician responses were received on more than 85% of sampled patients.

Comorbid conditions at the time of hospitalization for the most definitive treatment, usually surgery, were abstracted from the medical record. Patient comorbidity was assessed using the Charlson comorbidity index (23).

Analysis

Weighted proportions and means were used to examine trends in the receipt of adjuvant chemotherapy among stages II and III colon cancer patients and preoperative or postoperative radiation among stages II and III rectal cancer patients. We considered patients who received therapy or were recommended but it was unknown whether they received therapy as having received treatment in the analysis. Patients who refused chemotherapy (n = 148) or radiation therapy (n = 26) were not considered to have received therapy. We also examined the proportion of patients who received common chemotherapy agents and combination chemotherapy regimens. Although there is a lack of consensus on the use of chemotherapy for stage II colon cancer, we included these patients in select tables. In addition, we examined the proportion of rectal cancer patients who received any chemoradiation (ie, receipt of both chemotherapy and radiation at any point during the course of treatment) and various combinations of multimodality therapy.

Proportions and means were calculated with stratum-specific sample weights to account for the complex survey design. The proportions reported are weighted to reflect the population from which the sample was drawn. Sample weights were calculated as the inverse of the sampling proportion for each sampling stratum.

We used log-binomial regression models with stratum-specific sample weights to explore factors associated with receipt of adjuvant chemotherapy among stage III colon cancer patients and chemoradiation (preoperative or postoperative) among stages II and III rectal cancer patients. Sensitivity analyses considering differential registry participation by year and variation in the receipt of therapy by geographic region did not appreciably affect the results (not shown); therefore, we report the results of the overall analysis. Adjusted associations between covariates and receipt of therapy are reported as risk ratios and 95% confidence intervals.

Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC) and SUDAAN version 11.0.1 (Research Triangle Institute, Raleigh, NC). All statistical tests were two-sided.

Results

Characteristics of the study population (n = 7057) by year of diagnosis are shown in Table 1. Overall, 28.7% and 65.4% of stage II and III colon cancer patients received adjuvant chemotherapy, respectively (Table 2). Chemotherapy use increased among both stages from 1990 or 1991 (stage II: 22.5%; stage III: 56.3%)

Table 1. Characteristics of stages II and III colorectal cancer patients by year of diagnosis (n = 7057)*

	Year of diagnosis				
	1990/1991 (n = 2013)	1995 (n = 1114)	2000 (n = 876)	2005 (n = 1602)	2010 (n = 1452)
Characteristics	No. (wt %)	No. (wt %)	No. (wt %)	No. (wt %)	No. (wt %)
Sociodemographic characteristics					
Sex					
Male	1087 (49.5)	541 (48.2)	447 (49.9)	834 (50.5)	731 (51.1)
Female	926 (50.5)	573 (51.8)	429 (50.1)	768 (49.5)	721 (48.9)
Age at diagnosis, mean (SD), y	70.0 (0.30)	69.2 (0.59)	69.3 (0.60)	67.2 (0.61)	66.5 (0.60)
<55	254 (10.4)	186 (13.8)	188 (13.6)	419 (19.9)	395 (21.0)
55–64	406 (18.0)	246 (19.0)	187 (20.8)	366 (20.4)	345 (23.7)
65–74	671 (33.8)	341 (30.0)	237 (27.0)	369 (23.9)	339 (21.5)
75–79	287 (15.3)	149 (15.4)	105 (13.0)	185 (14.7)	144 (11.4)
≥80	395 (22.5)	192 (21.9)	159 (25.6)	263 (21.1)	229 (22.4)
Race/ethnicity					
White non-Hispanic	1731 (87.6)	564 (81.1)	329 (73.2)	568 (70.7)	466 (68.0)
Black non-Hispanic	163 (7.3)	273 (10.8)	197 (9.1)	351 (9.9)	356 (9.8)
Hispanic	64 (2.7)	277 (8.1)	168 (8.1)	324 (10.3)	301 (12.7)
Other	55 (2.3)	0	182 (9.6)	359 (9.0)	329 (9.4)
Health insurance					
Private/HMO/VA/Other	1520 (75.1)	782 (74.6)	539 (66.2)	1047 (73.0)	910 (65.6)
Medicaid	74 (3.5)	115 (6.2)	137 (9.9)	246 (10.2)	310 (16.8)
Medicare	315 (17.1)	149 (13.0)	147 (19.5)	228 (14.5)	147 (11.9)
None	31 (1.4)	38 (2.8)	32 (2.2)	65 (1.7)	69 (3.9)
Unknown	73 (2.9)	30 (3.3)	21 (2.2)	16 (0.6)	16 (1.8)
Marital status					
Married	1232 (57.7)	611 (55.1)	477 (55.0)	876 (50.6)	749 (53.2)
Not married†	744 (40.3)	485 (43.1)	368 (42.0)	692 (47.4)	639 (42.5)
Unknown	37 (2.0)	18 (1.8)	31 (3.0)	34 (1.9)	64 (4.3)
Comorbidity score					
0	1507 (74.1)	776 (70.6)	666 (74.0)	1132 (70.1)	963 (66.7)
1	408 (20.9)	274 (25.0)	163 (21.0)	373 (23.5)	386 (26.2)
≥2	98 (5.0)	64 (4.5)	47 (5.0)	97 (6.4)	103 (7.1)
Tumor characteristics					
Site					
Colon	1080 (77.4)	631 (77.6)	494 (75.2)	920 (72.8)	740 (71.4)
Rectum‡	933 (22.6)	483 (22.4)	382 (24.8)	682 (27.2)	712 (28.6)
Stage§					
II	974 (58.7)	564 (55.5)	372 (40.7)	829 (50.9)	723 (49.1)
III	1039 (41.3)	550 (44.5)	504 (59.3)	773 (49.1)	729 (50.9)
Number of positive lymph nodes (stage III only), mean (SD)	3.2 (0.10)	3.6 (0.23)	3.6 (0.24)	3.5 (0.19)	3.2 (0.19)
Histologic grade					
Well differentiated	176 (8.6)	55 (6.9)	43 (5.2)	94 (8.5)	70 (4.8)
Moderately differentiated	1328 (66.3)	796 (67.0)	599 (65.7)	1133 (66.0)	1037 (71.5)
Poorly differentiated	354 (17.1)	217 (21.9)	194 (25.0)	289 (21.6)	232 (17.2)
Undifferentiated	17 (1.0)	8 (1.2)	8 (1.1)	20 (1.6)	46 (3.3)
Unknown	138 (7.0)	38 (3.0)	32 (2.9)	66 (2.3)	63 (3.2)
Clinical trial participation					
No	1461 (75.6)	805 (76.5)	846 (96.1)	1471 (88.5)	1407 (96.4)
Yes	165 (7.0)	49 (3.0)	20 (3.1)	76 (4.9)	11 (0.5)
Unknown	387 (17.4)	260 (20.4)	10 (0.9)	55 (6.6)	34 (3.1)

* Percentages and means weighted by sampling fraction. Missing or unknown values included in proportions. wt = weighted.
† Not married includes single, divorced, separated, and widowed.
‡ Rectum includes tumors in the rectum or rectosigmoid junction.
§ Patients diagnosed in 1990 or 1991, 1995, and 2000 were sampled based on Extent of Disease (EOD) 10 coding, and patients diagnosed in 2005 and 2010 were sampled based on Collaborative Staging (CS) coding. TNM staging was derived by mapping T and N status from EOD and CS coding. Stage II included T3 or T4 tumors with no positive regional lymph nodes, and stage III included any T1 to T4 tumors with regional lymph node involvement. Stage definitions also correspond approximately to stage B2 and C of the Aster-Coller modification of Duke's original staging system.

to 2005 (stage II: 32.1%; stage III: 72.4%) and slightly decreased in 2010 (stage II: 29.3%; stage III: 66.4%). Receipt differed by age at diagnosis among stage II patients, with increases in receipt of therapy between 1990 or 1991 and 2000 in the 55 to 64 and 65 to 74 year age groups (Supplementary Figure 1, available online). There were also differences in receipt of adjuvant chemotherapy

Table 2. Proportion of stages II and III colon cancer patients who received adjuvant chemotherapy by stage at diagnosis (n = 3757)*

	Proportion of patients receiving chemotherapy			
	Stage II (n = 1908)		Stage III (n = 1849)	
Characteristics	wt %	95 % CI	wt %	95% CI
Overall	28.7	25.4 to 32.3	65.4	61.8 to 68.9
Year of diagnosis				
1990/1991	22.5	19.0 to 26.4	56.3	51.0 to 61.4
1995	27.9	21.2 to 35.6	59.5	48.6 to 69.6
2000	33.5	24.4 to 44.2	65.3	56.2 to 73.4
2005	32.1	24.8 to 40.5	72.4	65.1 to 78.7
2010	29.3	21.8 to 38.2	66.4	58.2 to 73.7
Age at diagnosis, y				
<55	59.5	48.6 to 69.5	84.5	78.6 to 89.0
55–64	46.2	38.4 to 54.2	84.9	79.3 to 89.2
65–74	29.9	23.9 to 36.6	72.9	65.4 to 79.3
75–79	17.3	11.3 to 25.4	63.0	54.0 to 71.2
≥80	5.8	3.6 to 9.0	30.3	21.9 to 40.3
Race/ethnicity				
White non-Hispanic	28.1	23.9 to 32.6	65.5	60.8 to 70.0
Black non-Hispanic	28.8	23.5 to 34.8	60.8	54.8 to 66.6
Hispanic	34.4	27.3 to 42.3	65.0	54.7 to 74.1
Other	29.8	23.0 to 37.6	71.0	62.1 to 78.6
Health insurance				
Private/HMO/VA/Other	31.2	26.9 to 35.7	67.0	62.7 to 71.1
Medicaid	24.2	15.8 to 35.2	61.4	51.8 to 70.2
Medicare	18.5	12.6 to 26.3	57.9	47.7 to 67.5
None	43.3	28.0 to 60.0	73.6	55.2 to 86.3
Unknown	39.9	19.8 to 64.2	76.0	50.6 to 90.7
Comorbidity score				
0	31.5	27.4 to 36.0	68.5	64.3 to 72.4
1	23.1	17.2 to 30.4	64.0	56.5 to 70.9
≥2	16.8	7.2 to 34.2	33.6	22.0 to 47.6
Tumor extent				
T1-2	NA	NA	76.9	66.9 to 84.5
T3	24.8	21.7 to 28.3	65.4	61.4 to 69.2
T4	53.6	41.7 to 65.2	58.0	47.6 to 67.8
Histologic grade				
Well/moderately differentiated	28.7	25.4 to 32.3	67.1	62.8 to 71.2
Poorly/undifferentiated	27.3	20.2 to 35.7	61.2	53.7 to 68.2
Unknown	37.6	24.2 to 53.2	65.0	49.8 to 77.6
Positive margins at surgery				
Yes	49.1	27.7 to 70.8	53.8	36.9 to 69.8
No	28.3	24.7 to 32.2	66.5	62.8 to 69.9
Unknown	24.7	17.4 to 33.9	62.2	47.1 to 75.3

* Proportions weighted by sampling fraction. Table excludes patients who did not undergo cancer-directed surgery (n = 20) or with missing or unknown chemotherapy agents (n = 82); patients who received preoperative chemotherapy (n = 6) are included. CI = confidence interval; NA = not applicable; wt = weighted.

for stage III patients by age and comorbidity (Figure 1). Receipt was highest among younger age groups (age <55 years, 84.5%; age 55–64 years, 84.9%) and patients with a comorbidity score of 0 (68.5%). A substantially smaller proportion of patients over the age of 80 years received chemotherapy in all study years (Supplementary Figure 2, available online).

Among stage III patients who received chemotherapy, there was a rapid increase in the use of oxaliplatin (5.5% in 2000 to 78.1% in 2010) and capecitabine (3.0% in 2000 to 23.6% in 2010), with a parallel decrease in the use of any 5-FU (98.8% in 1990 or 1991 to 79.3% in 2010) (Table 3). The majority of patients diagnosed in 1990 or 1991 (56.4%) and 1995 (53.3%) received 5-FU and levamisole, whereas patients diagnosed in 2010 were predominantly treated with FOLFOX (72.6%). A growing number of patients were treated with capecitabine alone (12.1% in 2010) or in combination with oxaliplatin (ie, CapeOx) (4.3% in 2010).

The proportion of stages II and III rectal cancer patients who received any radiation therapy (preoperative or postoperative) increased from 45.5% in 1990 or 1991 to 66.1% in 2010 (Figure 2). Receipt of any radiation therapy was higher among younger patients (age <55 years, 74.4%) compared with older patients (age ≥80 years, 25.1%) and among patients with a comorbidity score of 0 (60.4%) compared with patients with a comorbidity score of 2 or higher (53.4%). During the study period, 31.6% of patients received postoperative radiation therapy and 27.3% received preoperative radiation (Table 4). Receipt of preoperative radiation substantially increased over time, from 2.8% in 1990 or 1991 to 47.3% in 2010. The proportion of patients who received postoperative radiation increased from 1990 or 1991 (42.7%) to 1995 (51.3%) and subsequently decreased through 2010 (18.8%).

Receipt of chemoradiation for rectal cancer increased from 37.2% in 1990 or 1991 to 66.6% in 2010 (Supplementary Figure 3,

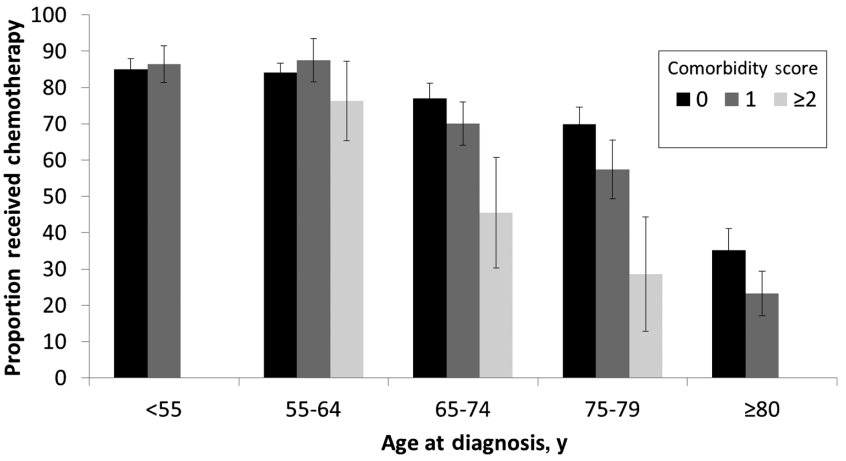

Figure 1. Proportion of stage III colon cancer patients diagnosed between 1990 and 2010 who received adjuvant chemotherapy by comorbidity score and age at diagnosis (n = 1849). Proportions weighted by sampling fraction. Figure excludes patients who did not undergo cancer-directed surgery (n = 9) or with missing or unknown chemotherapy agents (n = 82). Comorbidity score (CS) greater than 2 not shown for ages <55 and ≥80 years because of small number of observations (n < 5).

Table 3. Receipt of select chemotherapy agents and combination chemotherapy among stage III colon cancer patients treated with adjuvant chemotherapy by year of diagnosis (n = 1205) (not mutually exclusive categories)*

	Year of diagnosis				
	1990/1991 (n = 286)	1995 (n = 185)	2000 (n = 162)	2005 (n = 306)	2010 (n = 266)
Chemotherapy agent (any)	wt %	wt %	wt %	wt %	wt %
5-FU	98.8	99.9	96.9	88.6	79.3
Leucovorin	33.1	42.9	87.1	83.9	77.4
Levamisole	70.5	73.3	2.3	3.9	0.6
Bevacizumab	†	†	†	16.1	6.3
Capecitabine	†	†	3.0	15.5	23.6
Cetuximab	†	†	†	5.5	1.5
Irinotecan	†	†	8.0	10.1	6.1
Oxaliplatin	†	†	5.5	69.0	78.1
Other‡	6.9	2.0	6.2	7.6	4.1
Chemotherapy regimen					
5-FU alone	8.6	2.8	8.2	2.1	1.3
5-FU + leucovorin (only)	17.4	22.7	76.3	17.6	4.7
5-FU + levamisole (only)	56.4	53.3	0	0	0
FOLFOX (any)	†	†	5.5	62.9	72.6
FOLFIRI (any)	†	†	7.5	9.6	4.7
Capecitabine alone	†	†	0.2	3.6	12.1
CapeOx (only)	†	†	0	3.1	4.3

* Proportions weighted by sampling fraction and not mutually exclusive. 5-FU = 5-fluorouracil; CapeOx = capecitabine + oxaliplatin; FOLFIRI = 5-FU + leucovorin + irinotecan; FOLFOX = 5-FU + leucovorin + oxaliplatin; wt = weighted.
† No patient in our dataset received bevacizumab, cetuximab, capectiabine, irinotecan, or oxaliplatin in these years.
‡ Other includes less frequently administered chemotherapy agents, including methyl CCNU, CCNU, vincristine, PALA, UFT, methotrexate, and BCNU.

available online); however, the sequencing of radiation and chemotherapy differed by year of diagnosis (Table 5). The use of surgery followed by postoperative chemoradiation increased from 35.2% in 1990 or 1991 to 45.1% in 1995 and decreased from 2000 (41.6%) to 2010 (18.7%). The proportion of patients who received preoperative chemoradiation followed by surgery increased over the study period. From 2005 to 2010, the receipt of preoperative chemoradiation followed by surgery and postoperative chemotherapy nearly doubled (11.2% in 2005 to 20.8% in 2010). Among chemotherapy treated patients (preoperative, postoperative, or both), the use of 5-FU alone decreased from 38.3% in 1990 or 1991 to 10.3% in 2010, and there was an increase in the use of capectiabine alone (0.5% in 2000 to 20.8% in 2010) (Table 5). Similarly, the proportion of patients who received FOLFOX increased from 2005 (32.3%) to 2010 (44.0%).

In the log-binomial regression models, being diagnosed in year 2000 (risk ratio [RR] = 1.17, 95% confidence interval [CI] = 1.03 to 1.34), 2005 (RR = 1.26, 95% CI = 1.15 to 1.39), and 2010 (RR = 1.24, 95% CI = 1.12 to 1.37) was associated with receipt of chemotherapy among stage III colon cancer patients compared with being diagnosed in 1990 or 1991 (Table 6). Increasing age (75–79 years: RR = 0.81, 95% CI = 0.71 to 0.91; ≥80 years: RR = 0.37, 95% CI = 0.28 to 0.47), black (RR = 0.80, 95% CI = 0.71 to 0.91) and Hispanic (RR = 0.80, 95% CI = 0.67 to 0.97) race/ethnicity, and a

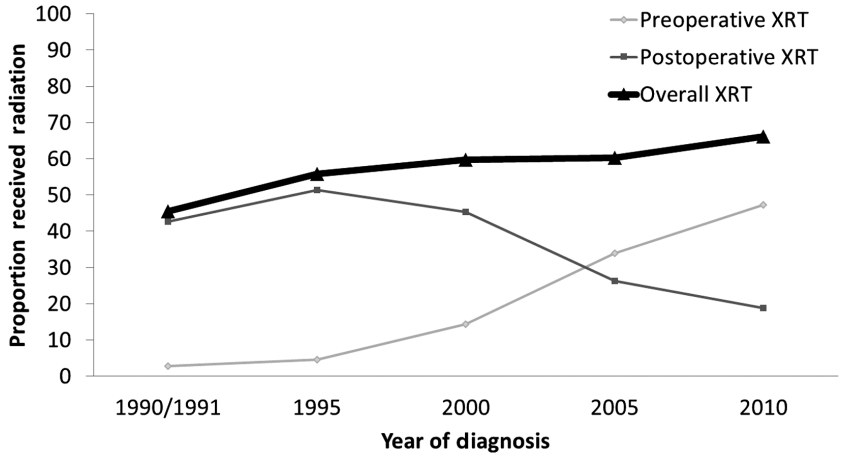

Figure 2. Proportion of stages II and III rectal cancer patients who received preoperative or postoperative radiation therapy by year of diagnosis (n = 3016). Proportions weighted by sampling fraction. Figure excludes patients who did not undergo cancer-directed surgery (n = 145), received intraoperative radiation (n = 1), received both preoperative and postoperative radiation (n = 15), and those in whom a radiation sequence could not be determined (n = 13). XRT = radiation therapy.

comorbidity score of 2 or greater (RR = 0.56, 95% CI = 0.35 to 0.87) were associated with not receiving chemotherapy. Among stages II and III rectal cancer patients, being diagnosed in 1995 (RR = 1.36, 95% CI = 1.17 to 1.58), 2000 (RR = 1.40, 95% CI = 1.19 to 1.65), 2005 (RR = 1.40, 95% CI = 1.21 to 1.63) or 2010 (RR = 1.59, 95% CI = 1.38 to 1.84) was associated with receipt of any chemoradiation (preoperative or postoperative) compared with being diagnosed in 1990 or 1991 (Table 6). Increasing age (65–74 years: RR = 0.87, 95% CI = 0.78 to 0.98; 75–79 years: RR = 0.59, 95% CI = 0.47 to 0.74; ≥80 years: RR = 0.33, 95% CI = 0.25 to 0.45) was associated with not receiving chemoradiation.

Discussion

Our results demonstrate that receipt of adjuvant chemotherapy for colon cancer gradually increased starting in 1990, which coincides with the publication of major findings from large, randomized trials (4) and recommendations of the National Institutes of Health Consensus Conference (3). Consistent with guidelines (24–28), the majority of stage III patients in our study received chemotherapy, but there were some marked disparities by age and comorbidity. As noted by others, older patients and those with high comorbidity are less likely to receive chemotherapy (29–34). Some physicians may not endorse adjuvant therapy for select patients because the expected gains in overall survival do not outweigh the potential harms to quality of life. Older patients and those with multiple comorbidities may not wish to pursue aggressive treatment. Further, there may be uncertainty regarding appropriate treatment strategies for older patients because they have historically been excluded from clinical trials (35).

Despite the uncertainty of evidence surrounding the use of adjuvant chemotherapy for stage II colon cancer, stage II patients frequently received chemotherapy during the study period. Almost one-third of all stage II patients, and more than 60% of younger patients (<55 years) with stage II disease, were treated with chemotherapy. These results are consistent with other studies that suggest that a large proportion of stage II colon cancer patients receive chemotherapy (30,36–39) and that receipt differs by age and comorbidity (29,30,36,37). Although some early trials have suggested a similar reduction in risk of recurrence for stage II and III patients treated with chemotherapy (40–42), past and current guidelines recommend against chemotherapy for stage II disease (3,24–28), based on cumulative evidence from meta-analyses (9,43). The proportion of stage II patients treated with chemotherapy in our study may be a result of both overtreatment of normal-risk and appropriate treatment of high-risk patients. Stage II patients with high-risk features (eg, T4 tumors, poorly differentiated histology, lymphovascular invasion) can be considered for adjuvant therapy, and we observed a larger proportion of stage II patients with T4 tumors or positive surgical margins treated with chemotherapy. However, only a small minority of stage II patients who received chemotherapy could be classified as high-risk. Our findings support the need for additional trials to identify subgroups of stage II colon cancer patients who are most likely to benefit from adjuvant chemotherapy.

Our results also highlight the rapid diffusion of newer therapies into community settings. Nearly 80% of all chemotherapy-treated patients with stage III colon cancer received oxaliplatin in 2010, compared with just 5% in 2000. This increase corresponds to a shift in evidence in favor of adding adjuvant oxaliplatin to 5-FU and its approval by the US Food and Drug Administration in 2004. Results of the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin (MOSAIC) trial showed an additional 23% reduction in risk of recurrence among patients treated with FOLFOX compared with those treated with 5-FU and leucovorin alone (8,44). The increased use of oxaliplatin in our study also highlights contemporary controversy regarding the use of therapy in older patients. Although the MOSAIC trial and numerous other studies (45–48) support the use of oxaliplatin for stage III colon cancer, only a small proportion of patients enrolled in these trials were older than 70 years. More recently, studies suggest there is little or no survival benefit of adjuvant oxaliplatin for older patients (49,50), and current guidelines (25) recommend against routine use in these patients (>70 years). However, the increasing use of oxaliplatin observed in our study, combined with the findings of others (51), may suggest oxaliplatin is still widely used in this population subgroup. Because uncertainty remains regarding the role of oxaliplatin in older patients, careful consideration must be given to the potential survival benefit in conjunction with patient preferences, cost, and risk of adverse events.

Similarly, we observed an increase in the use of capecitabine, either alone or in combination with oxaliplatin, from 2000 through 2010. Capecitabine was approved as an oral alternative

Table 4. Proportion of stages II and III rectal cancer patients who received preoperative or postoperative radiation therapy (n = 3016)*

	Proportion of patients receiving therapy			
	Postoperative radiation		Preoperative radiation	
Characteristics	wt %	95% CI	wt %	95% CI
Overall	31.6	29.1 to 34.1	27.3	24.7 to 30.0
Stage				
II	27.6	24.4 to 31.1	27.2	23.6 to 31.1
III	34.8	31.2 to 38.5	27.3	23.7 to 31.2
Year of diagnosis				
1990/1991	42.7	39.3 to 46.2	2.8	1.7 to 4.5
1995	51.3	46.4 to 56.3	4.6	2.9 to 7.2
2000	45.3	37.3 to 53.4	14.4	10.4 to 19.6
2005	26.3	21.5 to 31.8	33.8	27.9 to 40.4
2010	18.8	14.6 to 23.9	47.3	41.7 to 52.9
Age at diagnosis, y				
<55	30.6	25.9 to 35.7	43.8	37.7 to 50.2
55–64	36.1	30.4 to 42.1	29.9	24.9 to 35.5
65–74	35.0	30.5 to 39.8	24.8	20.3 to 29.8
75–79	30.4	23.3 to 38.6	15.7	10.0 to 23.9
≥80	18.6	12.8 to 26.2	6.5	3.8 to 10.8
Race/ethnicity				
White non-Hispanic	32.5	29.4 to 35.8	25.3	22.1 to 28.8
Black non-Hispanic	31.0	26.4 to 36.0	29.7	25.1 to 34.7
Hispanic	29.2	24.0 to 34.9	33.0	27.3 to 39.2
Other	26.5	21.5 to 32.1	36.1	29.9 to 42.7
Health insurance				
Private/HMO/VA/Other	33.0	30.2 to 36.0	27.3	24.2 to 30.7
Medicaid	25.5	18.6 to 33.8	36.0	28.2 to 44.6
Medicare	27.5	21.3 to 34.6	22.0	15.7 to 29.9
None	31.0	17.9 to 48.1	24.1	12.7 to 40.9
Unknown	33.9	22.9 to 47.0	6.9	2.0 to 21.2
Comorbidity score				
0	31.3	28.4 to 34.4	29.1	25.8 to 32.5
1	30.8	25.9 to 36.2	24.5	20.1 to 29.4
≥2	37.9	27.0 to 50.3	15.5	7.5 to 29.3
Chemotherapy†				
Yes	40.5	37.3 to 43.8	37.7	34.4 to 41.2
No	10.2	8.0 to 12.9	1.8	1.1 to 2.9
Unknown	6.6	2.8 to 14.6	5.9	2.1 to 15.1

* Proportions weighted by sampling fraction. Proportions combine across rows for total number of patients who received any radiation therapy. Table excludes patients who did not undergo cancer-directed surgery (n = 145), received intraoperative radiation (n = 1), received both preoperative and postoperative radiation (n = 17), and those in which a radiation sequence could not be determined (n = 13). CI = confidence interval; wt = weighted.
† Chemotherapy includes any chemotherapy received preoperatively, postoperatively, or both.

to 5-FU after phase III trial data showed equivalent disease-free survival, improved relapse-free survival, and fewer adverse events when comparing oral capecitabine to 5-FU and leucovorin (7). Our data provide support for a substitution effect, whereby the number of patients treated with capecitabine increased as the use of 5-FU simultaneously decreased. Capecitabine use has traditionally been difficult to measure on a population level because it is frequently underreported in Medicare claims data (52). This may be because claims data capture drug dispensing that generates a claim for reimbursement and do not capture information on prescribing. Differences between prescribing and dispensing may occur when patients decide not to fill the drug prescribed. One possibility is that patients with high copayments either do not fill capecitabine prescriptions (53) or receive the drug through pharmacy assistance programs, both of which are not captured in claims data. Given the limitations of administrative data sources, continuing to monitor treatment dispensing with capecitabine will likely remain a challenge. The unique features of our study design, particularly physician verification of therapy receipt, allowed us to provide a population-based estimate of capecitabine use.

While adjuvant chemotherapy for stage III colon cancer has been universally recommended by guidelines since 1990, the sequence and combination of therapies for rectal cancer have evolved over time and are reflected in our analysis. The proportion of patients who received preoperative radiation surpassed the proportion who received postoperative radiation in 2005. Also in 2005, patients treated with preoperative chemoradiation (with or without postoperative chemotherapy) exceeded the proportion treated with postoperative chemoradiation. These changes parallel results of the landmark German trial published in 2004 (15) that showed preoperative chemoradiation decreased the risk of local recurrence, improved sphincter preservation, and decreased treatment-related toxicities compared with postoperative therapy. Although earlier trials (13,14,17) and treatment guidelines (24) advocated preoperative therapy to

Table 5. Sequence of therapy and receipt of select chemotherapy agents among stages II and III rectal cancer patients by year of diagnosis (n = 3000) (mutually exclusive categories)*

	Year of diagnosis				
	1990/1991 (n = 911)	1995 (n = 462)	2000 (n = 356)	2005 (n = 630)	2010 (n = 641)
Therapy sequence	wt %	wt %	wt %	wt %	wt %
Surgery alone	38.8	30.4	24.4	20.1	18.5
Surgery + postoperative radiation	7.0	4.7	3.0	2.2	0.3
Surgery + postoperative chemotherapy	12.5	12.2	14.3	17.8	13.6
Surgery + postoperative chemoradiation	35.2	45.1	41.6	24.2	18.7
Preoperative chemoradiation + surgery	0.9	3.8	13.3	22.8	24.2
Preoperative chemoradiation + surgery + postoperative chemotherapy	†	†	†	11.2	20.8
Chemotherapy agents‡					
5-FU alone	38.3	35.3	35.8	16.5	10.3
5-FU + leucovorin (only)	23.3	31.5	53.9	14.3	3.5
5-FU + levamisole (only)	25.3	14.9	1.1	0	0
FOLFOX (any)	†	†	0	32.3	44.0
FOLFIRI (any)	†	†	5.1	3.3	6.3
Capecitabine alone	†	†	0.5	10.7	20.8
CapeOx (only)	†	†	0	6.1	5.9

* Proportions weighted by sampling fraction. Percentages do not add to 100 because of infrequently administered treatment sequences (eg, preoperative radiation + surgery). Table excludes patients who did not undergo cancer-directed surgery (n = 145) and with unknown or missing chemotherapy agents (n = 47). Patients with unknown or missing dates of chemotherapy or surgery (n = 25) and unknown radiation and surgery sequence (n = 9) are excluded from the proportions of therapy sequences, including chemotherapy or radiation. 5-FU = 5-fluorouracil; CapeOx = capecitabine + oxaliplatin; FOLFIRI = 5-FU + leucovorin + irinotecan; FOLFOX = 5-FU + leucovorin + oxaliplatin; wt = weighted.

† Preoperative chemoradiation + surgery + postoperative chemotherapy not measured, and no patient in our dataset received FOLFOX, FOLFIRI, capecitabine, and CapeOx in these years.

‡ Chemotherapy agents limited to patients who received any chemotherapy (n = 2039) and include chemotherapy delivered preoperatively, postoperatively, or both.

decrease the volume of the primary tumor, our results suggest that clinical practices did not shift toward preoperative treatment until after 2000.

The large increase in the proportion of rectal cancer patients treated with preoperative chemoradiation followed by surgery and postoperative chemotherapy in our study reflects the controversy surrounding the use of postoperative chemotherapy in this population. Although US guidelines advocate for the addition of postoperative chemotherapy to preoperative chemoradiation and surgery (54,55), some randomized trials reported no survival benefit (56–59). Long-term results of the EORTC 22921 trial suggested no difference in 10-year overall survival for patients treated with preoperative chemoradiation and postoperative chemotherapy compared with those treated with preoperative chemoradiation and surgery (56). However, a recent trial demonstrated improved disease-free survival with postoperative FOLFOX among rectal cancer patients treated with preoperative chemoradiation and surgery (60). Other studies (61,62) suggested that many rectal cancer patients treated with preoperative chemoradiation do not complete postoperative chemotherapy for reasons of age, performance status, pathological response, or surgical complications. Regardless of patient ability to tolerate additional therapy or response to preoperative treatment, the effect of postoperative chemotherapy remains unclear among patients previously treated with preoperative chemoradiation.

The differences we observed in the receipt of therapy for rectal cancer compared with colon cancer patients underscore inherent differences in the clinical behavior and treatment of these two distinct cancers. There was some difference in receipt of therapy by age and comorbidity for rectal cancer, but it was not as pronounced as the differences for colon cancer. For example, our results suggest a 30% difference in the proportion of stage III colon cancer patients with a comorbidity of 0 and greater than 2 who received chemotherapy compared with a difference of approximately 10% among rectal cancer patients receiving any radiation therapy. We also observed a lower receipt of adjuvant chemotherapy for black and Hispanic colon cancer patients compared with whites, but there was no racial disparity in chemoradiation receipt among rectal cancer patients. The modality of rectal cancer treatment changed frequently during the study period, and differential receipt of therapy by race may have been masked by changing treatment paradigms. In addition, although colon and rectal cancer share many features, there is an increased risk of local recurrence among rectal cancer patients. Preventing recurrence is a primary goal of therapy, which may explain why a larger number of older, high comorbidity, and minority rectal cancer patients received therapy.

Our study has several strengths. Patients were sampled by tumor site, sex, and age and oversampled by race/ethnicity to ensure adequate sample sizes that supported analyses by a variety of covariates. Detailed treatment information was available, including specific chemotherapy agents and treatment dates, which were verified by treating physicians and/or medical record review. Our results also complement randomized studies of treatment efficacy by demonstrating how changes in community practice have paralleled shifts in evidence from clinical trials.

A limitation of our analysis is the inability to fully explain trends and patterns of care observed during the study period that may be because of patient preferences or changes in healthcare delivery. For example, there was an overall decrease in the receipt of therapy among both colon and rectal cancer patients in 2010 that is likely not a result of differences in patient age or comorbidity. The decrease in therapy may instead be because of the increasing costs of CRC care (53,63–67) and the impact of the 2008 economic recession (eg, changes in insurance coverage,

Table 6. Adjusted risk ratios for the receipt of therapy among stage III colon and stages II and III rectal cancer patients (n = 4849)*

	Receipt of adjuvant chemotherapy for stage III colon cancer (n = 1849)	Receipt of chemoradiation† for stages II and III rectal cancer (n = 3000)
Variables	Adjusted‡ RR (95% CI)	Adjusted‡ RR (95% CI)
Year of diagnosis		
1990/1991	1.00	1.00
1995	1.07 (0.91 to 1.27)	1.36 (1.17 to 1.58)
2000	1.17 (1.03 to 1.34)	1.40 (1.19 to 1.65)
2005	1.26 (1.15 to 1.39)	1.40 (1.21 to 1.63)
2010	1.24 (1.12 to 1.37)	1.59 (1.38 to 1.84)
Age at diagnosis, y		
<55	1.00	1.00
55–64	1.03 (0.95 to 1.11)	0.93 (0.84 to 1.04)
65–74	0.89 (0.76 to 1.03)	0.87 (0.78 to 0.98)
75–79	0.81 (0.71 to 0.91)	0.59 (0.47 to 0.74)
≥80	0.37 (0.28 to 0.47)	0.33 (0.25 to 0.45)
Race/ethnicity		
White non-Hispanic	1.00	1.00
Black non-Hispanic	0.80 (0.71 to 0.91)	0.98 (0.89 to 1.07)
Hispanic	0.80 (0.67 to 0.97)	0.98 (0.87 to 1.11)
Other	0.92 (0.84 to 1.02)	1.00 (0.92 to 1.15)
Comorbidity score		
0	1.00	1.00
1	1.00 (0.96 to 1.04)	0.96 (0.87 to 1.06)
≥2	0.56 (0.35 to 0.87)	0.92 (0.75 to 1.13)
Health insurance		
Private/HMO/VA/Other	1.00	1.00
Medicaid	0.95 (0.83 to 1.09)	1.03 (0.92 to 1.15)
Medicare	0.98 (0.87 to 1.11)	1.07 (0.92 to 1.24)
None/unknown	0.99 (0.88 to 1.12)	0.79 (0.58 to 1.09)
Stage		
II		1.00
III		1.09 (0.99 to 1.20)

* Stage III colon cancer analysis excludes patients who did not undergo cancer-directed surgery (n = 9) or with missing or unknown chemotherapy agents (n = 82); stage II/III rectal cancer analysis excludes patients who did not undergo cancer-directed surgery (n = 145) or with unknown or missing chemotherapy agents (n = 47). CI = confidence interval; RR = risk ratio.

† Chemoradiation includes both chemotherapy and radiation therapy delivered in the preoperative or postoperative setting.

‡ Adjusted for all other variables shown in the table.

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copays, or cost sharing), which are not captured in the data. We also did not have a measure of performance status. Comorbidity score may account for some of the differences we observed in receipt of therapy, but performance status may further explain these differences. Finally, rates of physician verification were lower in 1990 or 1991 and 1995 than in other study years. We considered patients for whom therapy was recommended but it was unknown whether therapy was received as having received treatment in the analysis. Although there were few of these cases, our results may be slightly overestimated.

In summary, multiple randomized trials have demonstrated the efficacy of adjuvant therapies in improving the overall and disease-free survival of patients with locally advanced colorectal cancer. Our findings demonstrate increased adoption of adjuvant therapies for both colon and rectal cancer patients and differences in receipt of therapy by age, comorbidity, and year of diagnosis. Ongoing use of these therapies in community settings is critical to further reducing CRC mortality.

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