

Adjuvant Chemotherapy for Stage II Colon Cancer With Poor Prognostic Features

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See accompanying editorial on page 3346; listen to the podcast by Dr Saltz at www.jco.org/podcasts

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A B S T R A C T

Purpose

Adjuvant chemotherapy is typically considered for patients with stage II colon cancer characterized by poor prognostic features, including obstruction, perforation, emergent admission, T4 stage, resection of fewer than 12 lymph nodes, and poor histology. Despite frequent use, the survival advantage conferred on patients with stage II disease by chemotherapy is yet unproven. We sought to determine the overall survival benefit of chemotherapy among patients with stage II colon cancer having poor prognostic features.

Patients and Methods

A total of 43,032 Medicare beneficiaries who underwent colectomy for stage II and III primary colon adenocarcinoma diagnosed from 1992 to 2005 were identified from the Surveillance, Epidemiology, and End Results (SEER)–Medicare database. χ^2 and two-way analysis of variance were used to assess differences in patient- and disease-related characteristics. Five-year overall survival was examined using Kaplan-Meier survival analysis and Cox proportional hazards regression with propensity score weighting.

Results

Of the 24,847 patients with stage II cancer, 75% had one or more poor prognostic features. Adjuvant chemotherapy was received by 20% of patients with stage II disease and 57% of patients with stage III disease. After adjustment, 5-year survival benefit from chemotherapy was observed only for patients with stage III disease (hazard ratio [HR], 0.64; 95% CI, 0.60 to 0.67). No survival benefit was observed for patients with stage II cancer with no poor prognostic features (HR, 1.02; 95% CI, 0.84 to 1.25) or stage II cancer with any poor prognostic features (HR, 1.03; 95% CI, 0.94 to 1.13).

Conclusion

Among Medicare patients identified with stage II colon cancer, either with or without poor prognostic features, adjuvant chemotherapy did not substantially improve overall survival. This lack of benefit must be considered in treatment decisions for similar older adults with colon cancer.

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INTRODUCTION

Complete surgical resection is the primary treatment for patients with locoregional colon cancer (stage I, II, and III). Additional survival benefit from chemotherapy seems to be stage-specific: although patients with stage III (lymph-node positive) colon cancer enjoy a 10% absolute increase in 5-year survival after 6 months of fluorouracil-based chemotherapy, this same benefit has not been convincingly demonstrated in patients with stage II (node-negative) disease.¹⁻¹⁰ The commonly cited Quick and Simple and Reliable (QUASAR) prospective trial reported a pooled relative risk (RR) of death of

0.82 (95% CI, 0.70 to 0.95) for patients with stage I to III colon and rectal cancer receiving chemotherapy compared with surgery alone. However, it importantly failed to demonstrate a significant chemotherapy-related survival benefit for the stage II colon cancer subgroup (RR, 0.86; 95% CI, 0.66 to 1.12).⁸ In contrast, a more recent article that does report a survival advantage of chemotherapy for this population (hazard ratio [HR], 0.58; 95% CI, 0.48 to 0.71) required a meta-analysis combining data from five National Surgical Bowel and Breast Project trials reports to reach significance.¹¹ A larger meta-analysis of 12 clinical trials, including two of those cited in the Wilkinson study, was conducted as part

of developing the consensus recommendations from the American Society of Clinical Oncology. These recommendations conclude that existing trial data do not support routine use of chemotherapy in patients with stage II disease, citing a possible 2% to 4% increase in absolute survival, a statistically nonsignificant improvement.¹²

Despite its uncertain impact on survival, adjuvant chemotherapy administration is common, with one study identifying chemotherapy receipt among 27% of younger Medicare beneficiaries with stage II colon cancer.¹³ This practice is due to concerns that any potential benefit has been obscured by other factors, including insufficient patient numbers in clinical trials, good baseline prognosis, competing non-cancer-related deaths in the elderly population, and understaging of some patients with inadequate nodal resection.^{8,12,14,15} The American Society of Clinical Oncology guidelines suggest that certain poor prognostic features might reasonably prompt practitioners to consider therapy: elevated preoperative carcinoembryonic antigen (CEA) more than 5 ng/mL, diagnosis in the setting of bowel obstruction or perforation, need for emergent operation, T4 stage (extension to adjacent organs), inadequate nodal resection (< 12 nodes), or peritumoral lymphatic/venous invasion.^{12,14,16,17} However, there is no evidence that these characteristics, although associated with worse outcomes, are predictive of a successful response to adjuvant chemotherapy.^{12,17}

We hypothesized that patients with stage II colon cancer with poor prognostic features may demonstrate improved outcomes from adjuvant chemotherapy that were not observed in previous clinical trials due to insufficient power to detect clinically relevant change. To address this question, we examined the relationship between receipt of chemotherapy and 5-year overall survival among three groups of Medicare beneficiaries with colon cancer: stage II with no poor prognostic features, stage II with any poor prognostic features, and stage III. The purpose of the present study is to describe the effectiveness of chemotherapy in improving survival after surgical resection for this generalizable population of older adults.

PATIENTS AND METHODS

Data Sources

After the study protocol approval was obtained from the University of Wisconsin institutional review board with a waiver of consent, we used data

from the Surveillance, Epidemiology, and End Results (SEER) cancer registries linked to Medicare claims files to identify patients with a diagnosis of colon cancer. The SEER-Medicare data resource has been described previously by our group and others.¹⁸⁻²¹

Patient Selection

All Medicare-enrolled patients aged 66 years and older diagnosed with primary American Joint Committee on Cancer (AJCC) stage II or III colon adenocarcinoma within a SEER region during the years 1992 to 2005 were considered for study inclusion. Colon adenocarcinoma was identified by site and histology codes (codes for all variables, Appendix Table A1, online only). Those who underwent primary tumor resection with likely curative intent within 6 months of diagnosis were selected, excluding presumably palliative operations (eg, ostomy formation without colectomy). Continuous enrollment in Medicare Part A and Part B was required from 12 months preceding diagnosis through 5 years after discharge, death, or December 31, 2005 (whichever came first) to allow ascertainment of comorbidities, postoperative chemotherapy administration, and survival.

Exclusion criteria included health maintenance organization enrollment, unknown month of colon cancer diagnosis, diagnosis noted only on death certificate or autopsy report, or diagnosis of other malignancy within 1 year before the date of colon cancer diagnosis. From an initial cohort of 51,182 patients, the following patients were sequentially excluded: missing information (AJCC stage [n = 2,784], nodal assessment [n = 1,335], tumor stage or grade [n = 1,236]); initial cancer treatment other than surgery (preoperative radiation therapy [n = 44] or chemotherapy [n = 144]); or death before discharge from the surgical hospitalization (n = 146) or within 30 days of surgery (n = 2,461).

Variables

Outcome variable. The primary outcome measure for our study was 5-year overall mortality, defined as death within 5 years of primary surgery for colon cancer, based on dates of death recorded in the SEER Patient Entitlement and Diagnosis Summary File (PEDSF) according to Social Security Administration data.

Explanatory variable. The primary explanatory variable was receipt of adjuvant chemotherapy, based on previous work by Bradley et al²² and Dobie et al²³ defining postoperative chemotherapy in Medicare claims data. To avoid misclassification of chemotherapy for treatment of cancer recurrence as adjuvant chemotherapy, we considered only those claims within a designated treatment window, beginning with the date of primary surgery and ending with (1) claim date after which there were 3 months without colon cancer treatment, including chemotherapy or surgery; (2) evidence of distant cancer recurrence; or (3) 9 months after primary surgery, whichever came first.^{22,23} Patients with at least one claim in the treatment window were classified as having received chemotherapy.

Table 1. Propensity Score Models

	Stage II With No Poor Prognostic Features	Stage II With Any Poor Prognostic Features	Stage III
Main effect variables	Age Male Marital status Year of diagnosis Visit to oncologist within 30 days HCC score Hospitalizations in prior year In-hospital complications	Age Marital status Residence location Year of diagnosis Visit to oncologist within 30 days Census-tract median household income Census-tract education Hospitalizations in prior year In-hospital complications	Age Marital status Year of diagnosis Visit to oncologist within 30 days HCC score Hospitalizations in prior year Rehospitalizations within 30 days In-hospital complications
Interactions	Age*complication Marital status*male Age*oncologist visit	Age*oncologist visit Age*complication	Age*oncologist visit Age*complication Complication*oncologist visit Rehospitalization*oncologist visit

Abbreviation: HCC, Hierarchical Condition Categories.

Chemotherapy for Stage II Colon Cancer

Table 2. Characteristics of Medicare Beneficiaries Undergoing Resection for Stage II/III Colon Cancer

Characteristic	Stage II With No Poor Prognostic Features (n = 6,234)			Stage II With Any Poor Prognostic Features (n = 18,613)			Stage III (n = 18,185)		
	No Chemo (n = 5,057)	Chemo (n = 1,177)	P	No Chemo (n = 14,779)	Chemo (n = 3,834)	P	No Chemo (n = 7,817)	Chemo (n = 10,368)	P
Patient characteristics									
Age, years, %			< .001			< .001			< .001
65-69	10.2	25.4		7.7	21.6		5.0	19.4	
70-74	18.5	30.1		15.9	31.5		11.2	29.6	
75-79	24.7	28.8		23.1	28.0		20.2	29.0	
80-84	25.7	11.7		25.7	13.7		28.5	16.7	
85+	20.9	4.0		27.7	5.2		35.0	5.3	
Male sex, %	41.6	49.5	< .001	38.3	47.0	< .001	36.3	45.2	< .001
Race/ethnicity, %			.005			.09			< .001
White	86.8	86.2		87.0	86.7		83.9	84.8	
Black	5.8	4.1		6.2	5.4		8.0	6.3	
Asian or Pacific Islander	3.9	5.8		3.3	3.7		4.4	5.0	
Hispanic or other	3.5	4.0		3.6	4.2		3.7	4.0	
SEER registry, %			< .001			< .001			.02
California	27.2	29.1		29.1	27.6		28.0	26.9	
Connecticut	12.1	6.9		10.5	8.3		10.3	9.8	
Detroit	8.6	10.8		10.3	12.7		10.6	11.1	
Hawaii	2.4	2.6		1.2	1.0		1.9	2.0	
Iowa	12.6	13.0		14.7	13.6		13.0	12.2	
New Mexico	2.7	2.5		2.3	2.3		2.8	2.7	
Seattle	7.4	6.7		7.6	6.8		7.2	6.8	
Utah	3.4	3.1		2.7	2.4		3.4	3.4	
Atlanta and rural Georgia	4.0	4.8		3.8	4.1		3.9	3.9	
Kentucky	5.4	5.4		4.2	5.4		5.0	5.0	
Louisiana	4.0	4.3		4.1	5.0		3.9	4.6	
New Jersey	10.3	10.9		9.6	11.0		10.1	11.6	
Marital status, %			< .001			< .001			< .001
Married	50.1	64.9		44.1	59.7		39.2	59.4	
Widowed	35.3	21.7		40.8	25.7		45.1	25.9	
Single, separated, or divorced	11.4	10.9		12.0	11.5		12.5	11.9	
Unknown	3.2	2.6		3.1	3.1		3.1	2.8	
Residence location, %			.06			.005			.28
Major metropolitan	53.9	57.8		54.7	57.3		56.6	55.8	
Metropolitan or urban	35.5	32.2		34.6	31.9		32.7	33.8	
Less urban or rural	10.6	10.0		10.6	10.8		10.7	10.4	
Median household income (census tract), \$ in thousands*			.07			.01			< .001
Mean	46.7	48.1		44.0	45.1		43.4	46.1	
SD	23.3	23.9		21.7	22.1		21.0	22.5	
Less than 12-year education (census tract), %†			.97			.61			< .001
Mean	18.1	18.2		19.3	19.4		19.8	18.8	
SD	12.1	12.3		12.5	12.9		12.9	12.5	
HCC comorbidity score			< .001			< .001			< .001
Mean	1.8	1.5		2.1	1.9		2.9	2.3	
SD	1.2	1.1		1.4	1.2		1.6	1.3	
Tumor characteristics									
Year of diagnosis, %			< .001			< .001			< .001
1992-1995	18.5	16.9		23.2	21.3		22.6	18.2	
1996-1999	18.6	19.7		21.5	22.5		19.8	20.1	
2000-2002†	28.2	35.3		28.9	32.0		27.4	31.2	
2003-2005†	34.7	28.0		26.4	24.2		30.1	30.5	
Tumor location, %			.002			< .001			< .001
Right colon	64.2	60.0		54.3	50.2		58.2	56.6	
Transverse colon	10.1	8.6		11.8	10.8		10.9	9.1	
Left colon	8.1	9.8		10.1	11.0		9.2	9.2	
Sigmoid colon	16.0	20.0		22.4	26.4		20.0	23.5	
Unknown	1.6	1.7		1.5	1.6		1.7	1.6	

(continued on following page)

Table 2. Characteristics of Medicare Beneficiaries Undergoing Resection for Stage II/III Colon Cancer (continued)

Characteristic	Stage II With No Poor Prognostic Features (n = 6,234)			Stage II With Any Poor Prognostic Features (n = 18,613)			Stage III (n = 18,185)		
	No Chemo (n = 5,057)	Chemo (n = 1,177)	P	No Chemo (n = 14,779)	Chemo (n = 3,834)	P	No Chemo (n = 7,817)	Chemo (n = 10,368)	P
Comorbidity and treatment measures, %									
Any hospitalization in the previous year	28.1	19.0	< .001	29.1	21.0	< .001	32.7	22.0	< .001
Rehospitalization within 30 days of discharge	11.0	8.4	.009	12.8	9.2	< 0.001	16.1	8.8	< .001
Any in-hospital surgical complication	2.9	2.1	.14	4.1	4.1	.91	4.8	2.9	< .001
Oncologist visit within 30 days of surgery	21.9	54.7	< .001	23.3	54.6	< .001	28.1	58.3	< .001
Poor prognostic features, %									
Emergent admission	0.0	0.0		26.4	22.3	< .001	26.6	16.9	< .001
Intestinal obstruction on admission	0.0	0.0		6.1	6.9	.08	6.0	4.6	< .001
Intestinal perforation on admission	0.0	0.0		2.4	4.4	< .001	2.7	1.6	< .001
T stage						< .001			< .001
Tis, T0, T1, or T2	0.0	0.0		0.0	0.0		9.4	11.7	
T3	100.0	100.0		82.8	73.9		70.4	70.2	
T4	0.0	0.0		17.2	26.1		20.2	18.1	
No. of nodes resected, %						< .001			< .001
0-11	0.0	0.0		72.5	69.5		50.7	47.8	
≥ 12	100.0	100.0		27.5	30.5		49.3	52.2	
Tumor grade, %			.66			.001			.02
Well differentiated	8.5	8.1		7.4	6.9		4.8	5.0	
Moderately differentiated	91.5	91.9		66.4	64.1		62.5	64.3	
Poorly or undifferentiated	0.0	0.0		26.1	29.0		32.7	30.7	
No. of poor prognostic features, %						< .001			< .001
0	100.0	100.0		0.0	0.0		19.4	24.0	
1	0.0	0.0		60.5	56.5		39.0	43.2	
2	0.0	0.0		30.1	31.0		28.1	23.7	
3	0.0	0.0		7.9	10.7		10.9	7.6	
4, 5, or 6	0.0	0.0		1.6	1.9		2.7	1.6	

NOTE. Percentages may not sum to 100% due to rounding.

Abbreviations: Chemo, chemotherapy; SEER, Surveillance, Epidemiology, and End Results; SD, standard deviation; HCC, Hierarchical Condition Categories.

*A total of 2,243 individuals with missing data are not included in these means.

†Three SEER registries (Kentucky, Louisiana, New Jersey) were added in 2000.

Stratification variables. AJCC stage was identified from SEER data. Poor prognostic features identified from Medicare data included diagnosis in the setting of intestinal obstruction or perforation, emergent admission for surgery, T4 stage, poor/undifferentiated histology, and fewer than 12 lymph nodes examined.^{12,14,16,17} Other reported poor prognostic features (preoperative CEA level and peritumoral lymphatic/venous invasion) were not available in the SEER-Medicare data set.

Control variables. Date of birth, sex, race/ethnicity, and marital status were obtained from SEER data. Census tract-level median household income and level of education were obtained from the SEER PEDSF (Census 1990 data used for diagnosis years 1992 through 1999; Census 2000 data used for years 2000+) and used as proxies for patient socioeconomic status. Geographic region was represented by SEER registry and rural/urban county of residence on the basis of 2003 Rural/Urban Continuum Codes identified from the PEDSF. For risk adjustment, we used Centers for Medicare and Medicaid Services Hierarchical Condition Categories (HCC) based on outpatient and inpatient diagnoses from the 12 months before colon cancer diagnosis. The resulting score can be interpreted as a patient's predicted level of "future health care need," relative to the average Medicare beneficiary (HCC = 1.0).²⁴ We also identified Medicare claims for hospitalizations in the year before diagnosis, in-hospital complications, rehospitalizations, and oncologist visits within 30 days of discharge from the surgical stay. Year of diagnosis and tumor location were obtained using SEER data.

Statistical Analysis

We described the patient- and disease-related characteristics for each stage group by chemotherapy administration status and evaluated univariate statistical differences using χ^2 tests for categorical variables and two-way anal-

ysis of variance tests for continuous variables. Kaplan-Meier survival analysis techniques were used to compare 5-year overall survival between stage groups and by chemotherapy status within each stage group. Cox proportional hazards regression-based methods were used to determine adjusted HRs and 95% CIs of 5-year overall mortality in patients who did or did not receive chemotherapy within each stage group, controlling for patient- and disease-related covariates.

In clinical practice, significant differences exist between patients who are and are not treated with chemotherapy, particularly with regard to age, comorbidities, and provider/patient preferences. Propensity score techniques were used, as has been previously described, to address selection bias owing to nonrandom treatment assignment.²⁵⁻²⁹ Logistic regression models were built for each stage group to estimate each patient's probability of receiving adjuvant chemotherapy conditional on sociodemographic and clinical characteristics. These models included main effects and interaction terms as needed to produce balance of covariates across treated and nontreated strata with equivalent mean propensity scores, ρ (variables included in the final models, Table 1). The Cox regression models for each stage group were then weighted by $(1/\rho)$ for individuals receiving chemotherapy, and $(1/[1 - \rho])$ for nontreated individuals. For propensity score-based analyses, only subjects in the common support region were included.

Analyses were performed by the lead author using SAS 8.02 (SAS Institute, Cary, NC) and STATA 10.0 software (STATA, College Station, TX). All tests of significance used two-sided *P* values at the .05 level. Robust estimates of the SE were used in all regression analyses.

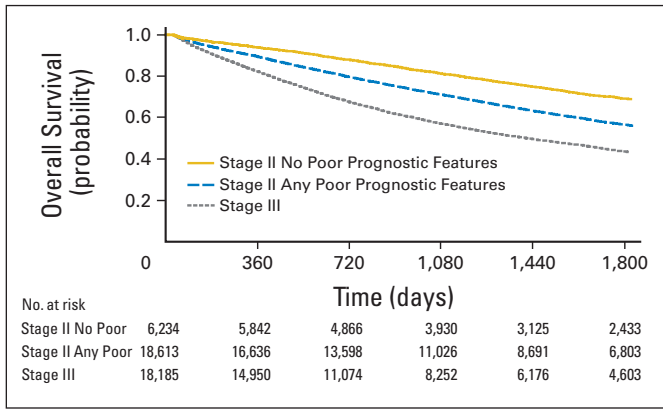


Fig 1. Overall survival by stage group (Kaplan-Meier). Cox regression-based test for equality of survival curves confirms significant differences between stage groups (likelihood-ratio $\chi^2 = 1540.59$; $P < .001$).

RESULTS

Receipt of Adjuvant Chemotherapy

We identified 43,032 individuals for inclusion in our study and stratified them into three analysis groups: stage II with no poor prognostic features (n = 6,234), stage II with any poor prognostic features (n = 18,613), and stage III (n = 18,185). Among the stage II with no poor prognostic features group, 19% received any adjuvant chemotherapy, compared with 21% of patients in the stage II with any poor prognostic features group and 57% of patients with stage III disease ($P < .001$). Among patients receiving chemotherapy, the mean number of months was 5.41 (95% CI, 5.37 to 5.45) for all patients, 5.17 (95% CI, 5.03 to 5.31) for stage II with no poor prognostic features, 5.12 (95% CI, 5.04 to 5.20) for stage II with any poor prognostic features, and 5.54 (95% CI, 5.49 to 5.59) for stage III.

Characteristics of Patients Receiving Chemotherapy

Table 2 compares the patient- and disease-related characteristics of individuals who did or did not receive chemotherapy within each stage group. Those who received chemotherapy were younger, more likely to be male or married, and had lower comorbidity, as measured by HCC, prior-year hospitalization, and 30-day rehospitalization after surgery. Although the majority of tumors were located in the right colon, as noted previously,^{30,31} a larger proportion of left-sided tumors were present among those receiving adjuvant chemotherapy. In all three stage groups, the proportion of individuals who had an oncologist visit within 30 days of surgery was significantly higher among those receiving chemotherapy.

In the stage II with any poor prognostic features group, higher proportions of patients with perforation, T4 stage, and poor histology were seen in the chemotherapy group compared with the no chemotherapy group. In contrast, equal or smaller proportions of patients with emergent admission, obstruction, or fewer than 12 nodes received chemotherapy.

Given the clear group differences by chemotherapy receipt, propensity scores describing the likelihood of chemotherapy receipt contingent on covariates were used to reweight the patient population for each stage group. Many distributional differences, such as age, were eliminated, yielding treated and untreated groups that were more similar, as would be anticipated in a randomized trial (Appendix Table A2, online only).

Survival Benefit of Chemotherapy

Kaplan-Meier unadjusted survival analysis was conducted to compare 5-year overall survival between the three stage groups (Fig 1). The presence of poor prognostic features identified a subgroup of stage II patients with significantly reduced survival at 5 years (stage II with no poor prognostic features, 69% [95% CI, 67.9% to 70.5%]; stage II with any poor prognostic features, 57% [95% CI, 55.8% to 57.4%]; stage III, 44% [95% CI, 42.8% to 44.4%]).

To examine the stage-specific survival benefit attributable to chemotherapy, we used Cox proportional hazards regression methods. We first examined the baseline model predicting 5-year overall mortality, including all covariates and a stage group-chemotherapy interaction term. This interaction was significant (likelihood-ratio $\chi^2 = 34.5$, $P < .0001$), suggesting that we should proceed with separate regression models by stage group (Table 3). The unadjusted models, containing chemotherapy as the explanatory variable, showed a significant survival benefit for all stage groups from adjuvant chemotherapy, as demonstrated by HRs less than 1.0. However, when important patient and disease characteristics were included as covariates, only the stage III group retained significant mortality reductions (HR, 0.64; 95% CI, 0.61 to 0.68). When propensity scores were included in the covariate-adjusted regression models as weights, the stage-specific 5-year survival benefit from chemotherapy remained unchanged, with a significant HR seen only for stage III patients (HR, 0.64; 95% CI, 0.60 to 0.67).

Kaplan-Meier survival analysis with propensity-score weighting was used to compare 5-year overall survival between treated and untreated patients in each stage group (Figs 2A through 2C). Given the sample size available for this analysis, we would have been able to detect an absolute difference in 5-year overall survival among the stage

Table 3. Overall 5-Year Mortality by Stage Group (Cox regression model)

Model	Stage II With No Poor Prognostic Features			Stage II With Any Poor Prognostic Features			Stage III		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Unadjusted	0.67	0.59 to 0.77	< .001	0.67	0.63 to 0.71	< .001	0.48	0.46 to 0.5	< .001
Adjusted for covariates*	1.05	0.9 to 1.22	.53	0.96	0.89 to 1.03	.24	0.64	0.61 to 0.68	< .001
Adjusted for covariates* with propensity score weighting	1.02	0.84 to 1.25	.80	1.03	0.94 to 1.13	.47	0.64	0.6 to 0.67	< .001

Abbreviation: HR, hazard ratio.

*Covariates: age, sex, ethnicity, marital status, Surveillance, Epidemiology, and End Results registry, residence location, tumor location, diagnosis year, census-tract median household income and education, Hierarchical Condition Categories score, prior-year hospitalizations, 30-day rehospitalizations, in-hospital complications, 30-day oncologist visits.

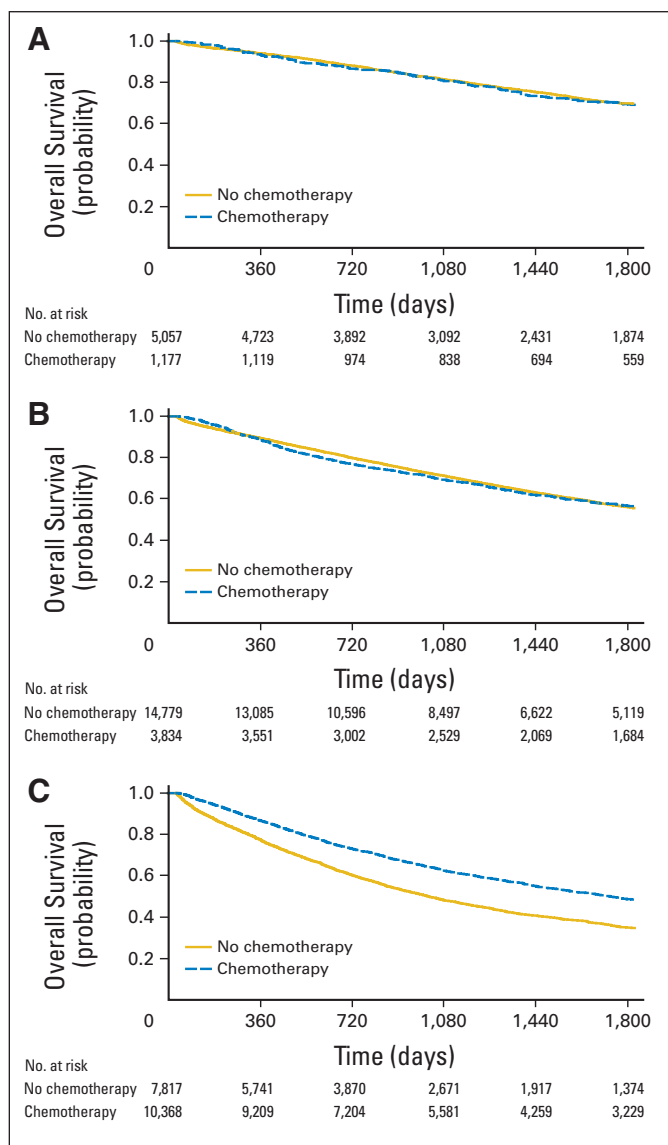


Fig 2. Overall survival by chemotherapy administration status and stage group (Kaplan-Meier) with propensity score weighting. Cox regression–based test for equality of survival curves: (A) stage II with no poor prognostic features: Wald $\chi^2 = 0.01$, $P = .94$; (B) stage II with any poor prognostic features: Wald $\chi^2 = 0.20$, $P = .65$; (C) stage III: Wald $\chi^2 = 232.80$, $P < .001$.

II with any poor prognostic features group of 2%. However, no difference in 5-year survival was observed between treated and untreated patients for this group (56.7% v 56.1%) or for stage II with no poor prognostic features (70.0% v 69.5%). In contrast, stage III patients derived significant survival benefit from chemotherapy (48.9% v 35.2%).

DISCUSSION

Our primary aim was to determine the degree of 5-year overall survival benefit conferred by adjuvant chemotherapy on patients with stage II colon cancer having poor prognostic features. Although these characteristics do distinguish a subgroup of stage II patients with worse survival than the rest of the stage II cohort, they do not predict

measurable mortality benefit from chemotherapy in this study population. Our sample size in this analysis of Medicare beneficiaries allows us to detect, if present, a 2% absolute difference in 5-year survival attributable to chemotherapy; our lack of statistical significance implies that any benefit that exists is quite small. Interestingly, chemotherapy use does not differ between stage II patients with or without poor prognostic features, suggesting that these are not central to the treatment decision.

Our analysis has several important advantages over prior investigations. In contrast to prior trials that predominantly recruited patients with stage III disease, our study population has sufficient power to detect clinically significant differences in survival for patients with stage II disease, addressing concerns about inadequate sample size. In addition, this is the only study to date that specifically examines the subgroup of stage II patients with poor prognostic features, thereby addressing the population heterogeneity that was thought to confound prior conclusions of minimal survival benefit.^{1-10,12,15} The median age of colon cancer diagnosis is 70 years, yet many older adults were explicitly excluded from randomized chemotherapy trials or were otherwise deemed ineligible as a result of age-related comorbidity, provider bias, or patient preference.¹⁻¹⁰ Our study population importantly presents a more real-world age distribution (68% over age 75 years at diagnosis) and includes patients with greater levels of comorbidity and risk than typically allowed in randomized trials, facilitating better generalizability to the population of senior adults.³² These factors, particularly our inclusion of older individuals and those with shorter postoperative survival compared with the Schrag studies, may explain the relatively low utilization of chemotherapy identified in our analysis, even among stage III patients.¹³

This investigation uses existing data to address a research question that would require substantial resources and time to answer through a randomized trial. Limitations to our study include our inability to investigate the role of two known poor prognostic features, preoperative CEA and lymphovascular invasion, as these characteristics are not available within the SEER-Medicare database. These features may represent more locally advanced disease, but it is unclear how they influence the likelihood of chemotherapy receipt and any subsequent survival benefit. Although our models included several important patient- and disease-related variables, administrative data lack direct measurement of factors that may influence treatment assignment, such as patient preferences or provider care patterns. There is some suggestion that chemotherapy administration is related to provider practice: Hershman et al³³ found that among elderly women with breast cancer, chemotherapy was more commonly received by those treated by younger private-practice oncologists. Although these factors may influence treatment receipt, their relationship to survival is unknown. Finally, our study examines only Medicare beneficiaries age 66 years and older at the time of diagnosis, limiting its applicability to younger patients with colon cancer, such as those with familial syndromes. However, because more than 60% of colorectal cancer diagnoses are made in the 65-years-and-older population, our findings are likely appropriate for the majority of patients with colon cancer.³²

This study retrospectively examines the use of chemotherapy as identified through Medicare claims data using a “one claim” algorithm.^{22,23} This creates a heterogeneous population in which some patients received a substandard duration of therapy for unrecorded reasons, possibly including patient/provider preference or adverse

effects, whereas other patients receive a complete course. We speculate that those patients who stop chemotherapy early may have other features related to poor survival (older age, comorbid conditions, and so on), and that the inclusion of both subsets of patients within a single analysis group likely leads to a reduction in the survival benefit observed with chemotherapy. However, the “none versus any” approach used to assign treatment status provides a window into the effectiveness of chemotherapy in real world practice, in which an individual’s likelihood of completing the treatment course is not known at the outset of the study. We also note that chemotherapeutic recommendations have changed since the time period of this analysis, and many patients in our study population likely did not receive oxaliplatin, thus limiting the applicability of our results to today’s standard regimens. Further investigation into patient characteristics predicting therapy completion, the influence of chemotherapy duration on survival, and the benefit of oxaliplatin in practice may be warranted.

The poor prognostic features considered in this analysis and described in published guidelines represent an imprecise clinical mechanism for identifying patients with high-risk stage II colon cancer. Recently, high-frequency DNA microsatellite instability from mismatch repair defects has emerged as an important predictor of better prognosis as well as resistance to fluorouracil therapy.^{12,34-37} Older patients may also demonstrate increased prevalence of a methylator phenotype (CIMP), which may be correlated with higher disease stages and sporadic cases of microsatellite instability.^{38,39} These and other histologic and genetic factors are the subject of investigation in ongoing basic science and prospective clinical trials that may identify any subset of stage II patients for whom chemotherapy offers significant survival benefit.⁴⁰

In conclusion, we find that patients with stage II colon cancer, even those with any of six identified poor prognostic features, do not have a significant survival benefit from chemotherapy. Given the

frequent use of chemotherapy in this generalizable population of older adults, this suggests that, in practice, many patients may be receiving chemotherapy with a disadvantageous risk-benefit ratio. Given the statistical power of this study, clinicians may wish to counsel high-risk older adults with colon cancer that any possible survival benefit is likely less than 2% at 5 years.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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