Original Contribution

Uptake of Oxaliplatin and Bevacizumab for Treatment of Node-Positive and Metastatic Colon Cancer

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Abstract

Purpose: In 2004, the US Food and Drug Administration approved bevacizumab and oxaliplatin for use in metastatic colon cancer and oxaliplatin for localized colon cancer. We investigated the diffusion and predictors of use of these medications in the year after approval.

Patients and Methods: We used the Surveillance, Epidemiology, and End Results–Medicare database to identify patients older than 65 years diagnosed with stages III and IV colon cancer in 2005. Characteristics of the treating oncologists were identified using the American Medical Association database. We used logistic regression and generalized estimating equations to analyze factors associated with bevacizumab and oxaliplatin use.

Results: Among 1,547 patients with stage III colon cancer who had claims submitted by oncologists, 801 (51.8%) received adjuvant chemotherapy, and of those, 432 (54.1%) received oxaliplatin, whereas 54 (6.7%) received off-label bevacizumab. Among 859 patients with stage IV disease who saw oncologists, 435 (50.6%) received chemotherapy, and of those, 310 (71.3%) received bevacizumab, 289 (66.4%) received oxaliplatin, and 357 (82.1%) received oxaliplatin and/or irinotecan. Older patient age and more comorbidities were associated with nonreceipt of oxaliplatin for stage III disease and oxaliplatin and/or irinotecan for stage IV disease. Having a physician who graduated medical school after 1975 predicted receipt of both adjuvant oxaliplatin (odds ratio [OR], 1.65; 95% CI, 1.11 to 2.45) and oxaliplatin and/or irinotecan for stage IV disease (OR, 2.43; 95% CI, 1.47 to 4.01). None of the factors analyzed predicted bevacizumab receipt.

Conclusion: Uptake of new chemotherapy drugs for patients diagnosed with stages III and IV colon cancer in 2005 was rapid. Physician characteristics were consistently associated with this uptake.

Introduction

During the last decade, significant progress has been made in the management of locally advanced and metastatic colon cancers. The addition of oxaliplatin to infusional fluorouracil (FU) and leucovorin decreases cancer recurrence and increases disease-free survival for patients with node-positive disease.[1] Patients with metastatic colon cancer also benefit from the addition of new combination therapies to FU plus leucovorin–based therapy. For example, FU plus leucovorin with irinotecan (FOLFIRI) improves survival in patients with metastatic disease,[2] as does oxaliplatin plus infusional FU plus leucovorin (FOLFOX) combinations.[3] Bevacizumab was the first monoclonal antibody to be approved in metastatic colon cancer, largely because of the overall survival benefit demonstrated with its addition to FU plus leucovorin plus irinotecan chemotherapy.[4] However, the benefit observed in the metastatic setting does not translate to a benefit in patients with localized disease.[5]

In 2004, the US Food and Drug Administration (FDA) approved oxaliplatin for first-line treatment of metastatic colorectal cancer (January 2004) and as adjuvant therapy for resected stage III colon cancer (November 2004).[6] The FDA also approved bevacizumab for use in metastatic colorectal cancer in February 2004.[6] FDA approval for irinotecan in metastatic colorectal cancer dates back to October 1998 as a second-line medication and April 2000 as first-line therapy.

In this study, we explore the uptake of oxaliplatin and bevacizumab in the community after the studies that demonstrated their efficacy and the approval of the FDA. We sought to determine what factors predicted increased use of these drugs in Medicare-age patients with stage III or metastatic colon cancer.

Patients and Methods

Study Database

We used the Surveillance, Epidemiology, and End-Results (SEER) –Medicare database, codeveloped by the National Cancer Institute and Center for Medicare and Medicaid Services. The SEER program represented roughly 14% of the US population in 1991, and since 2000, it has covered approximately 26% of the United States. Medicare covers hospital services, physician services, some drug therapy, and other medical services for more than 97% of persons older than 65 years. The linked SEER-Medicare database contains clinical, demographic, and medical claims data on patients older than 65 years and is a unique population-based resource for longitudinal epidemiologic and health outcomes studies. Its characteristics and validation have been reported elsewhere.[7,8]

To obtain information on the characteristics of the physicians who treated patients in the SEER-Medicare database, we used the unique physician identification numbers to link Medi-

care claims with the American Medical Association (AMA) master file, as described previously.[9] This file contains data collected from physician members of the AMA, including sex, age, medical degree (doctor of medicine [MD] or doctor of osteopathy [DO]), location of medical school (US *v* foreign school), year of graduation, employment setting (private *v* nonprivate), and specialty.[9] Physicians' records are continuously updated and verified by the AMA.[10]

Sample Selection

We identified all individuals in the SEER-Medicare database diagnosed with histologically confirmed primary adenocarcinoma of the colon at age 65 years or older who were not coenrolled in a health maintenance organization from 12 months before diagnosis throughout the study period and/or were not covered by Medicare Parts A and B at any point during that time period, leaving 5,495 patients.

For stage III disease, we further restricted selection by date of diagnosis between September 1, 2004, and December 31, 2005, who underwent potentially curative resections (n = 2,029). We excluded 68 patients treated with irinotecan, 11 patients treated with bevacizumab alone without additional chemotherapy, 33 patients treated with any other chemotherapy, and 33 patients initially treated with their first chemotherapy more than 182 days from diagnosis, leaving a sample population of 1,884 patients.

For stage IV disease, we included patients diagnosed between January 1, 2005, and December 31, 2005. We excluded eight patients treated with bevacizumab without additional chemotherapy and 15 patients treated with chemotherapy other than FU, irinotecan, or oxaliplatin, for a final cohort of 1,119 patients.

We used different dates of diagnosis for our two cohorts to maximize the sample size in each. Because adjuvant therapy is frequently not started until several months after diagnosis, we chose to include patients with stage III disease diagnosed up to 4 months before January 1, 2005.

The patients in each cohort were categorized by age group at diagnosis, race/ethnicity, sex, marital status, number of positive nodes, tumor grade (well or moderately differentiated or poorly differentiated), comorbidity score, and residence (metropolitan or nonmetropolitan). The physician with the most claims during our study period was selected as the patient's primary oncologist.

Treatment With FU, Oxaliplatin, Irinotecan, and Bevacizumab

Using Health Care Financing Administration codes and the Common Procedure Coding System (HCPCS), we identified patients who had received FU (level II HCPCS J9190), oxaliplatin (J9263), irinotecan (J9206), and/or bevacizumab (J9035) from diagnosis until the end of 2006. Patients with stage III disease who received any of the study medications within 180 days of their cancer diagnosis were classified as receiving adjuvant treatment. For patients who did not receive any of the four study medications, we assessed whether level II HCPCS codes or International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), diagnostic codes from their physician claims files showed evidence of other chemotherapy delivery. The validity of SEER-Medicare claims data for chemotherapy use in general, and for FU use in particular, has been described previously.[7]

Patient Socioeconomic Status

We generated an aggregate socioeconomic status (SES) score based on education, poverty, and income information from census data, following the method adapted by Du et al.[11] Patients were ranked on a scale of one to five, where one was the lowest, based on a formula incorporating these variables weighted equally.

Comorbid Disease

To assess the prevalence of comorbid disease, we used the Klabunde et al[12] adaptation of the Charlson comorbidity index.[13] Inpatient and outpatient claims were searched for ICD-9-CM diagnostic codes. Each condition was weighted, and patients were assigned a score based on the Klabunde-Charlson index.[12]

Statistical Analyses

The χ^2 test was used to compare oncologist-related, demographic, and clinical characteristics between patients who did and did not receive chemotherapy. Univariate odds ratios (ORs) were calculated individually for each variable. All hypothesis tests were two sided.

The generalized estimating equations (GEEs) methodology was introduced by Zeger et al[14] to deal with clustering in data that otherwise would be analyzed by a generalized linear model, and GEEs (PROC GENMOD, SAS statistical software [SAS Institute, Cary, NC]) have become an important strategy in analysis of correlated data.[15] We used GEEs to account for the correlations of outcome measures among patients who had the same physician. The unit of analysis was the patient. For each patient, the physician's unique physician identification number was used as the clustering variable. The model assumptions were that the data had a binomial distribution, the link function was logit, and the type of variance was exchangeable.

We evaluated the odds of chemotherapy for all the categories of each variable, controlling for all other variables in the model. The model included: oncologist characteristics (sex, type of degree, country of training, practice type, patient volume); patient demographic variables (age, race, place of residence, marital status, SES); and clinical variables (tumor grade, American Joint Committee on Cancer stage, comorbidity score). All statistical analyses were conducted using the SAS system for Windows (version 9.13; SAS Institute).

Results

Baseline Characteristics of Analysis Group

Of the 1,884 patients in our stage III cohort, 1,547 (82.1%) had a claim submitted by an oncologist. Of the 1,119 patients

Table 1. Patient and Oncologist Demographic and Clinical Characteristics*

Characteristic	Stage III (n = 1,547) No.	%	Stage IV (n = 859) No.	%
Patient				
Age at diagnosis, years				
65-69	244	15.8	141	16.4
70-74	310	20.0	198	23.0
75-79	392	25.3	201	23.4
80-84	348	22.5	181	21.1
≥ 85	253	16.4	138	16.1
Mean	77.5		77.2	
SD	6.94		7.08	
Sex				
Male	659	42.6	393	45.8
Female	888	57.4	466	54.2
Race				
White	1,300	84.0	708	82.4
Black	128	8.3	92	10.7
Hispanic	22	1.4	11	1.3
Other	97	6.3	48	5.6
Marital status				
Married	800	51.7	406	47.3
Single/divorced	695	44.9	427	49.7
Unknown	52	3.4	26	3.0
Urban/rural location				
Urban	1,376	88.9	778	90.6
SES, quintile				
Lowest	175	11.3	94	10.9
Second	294	19.0	167	19.4
Third	335	21.7	198	23.1
Fourth	352	22.8	182	21.2
Highest	391	25.3	218	25.4
Clinical				
Grade				
Well differentiated	76	4.9	32	3.7
Moderately differentiated	1,958	61.9	422	49.1
Poorly differentiated	456	29.5	218	25.4
Undifferentiated	34	2.2	13	1.5
Unknown	23	1.5	174	20.3
No. of comorbidities				
0	853	55.1	483	56.2
1	437	28.2	250	29.1
≥ 2	253	16.4	126	14.7
Hypertension				
No	461	29.8	274	31.9
Yes	1,086	70.2	585	68.1
Oncologist				
Sex				
Male	1,231	79.6	676	78.7
Female	316	20.4	183	21.3
Degree				
DO	55	3.6	28	3.3
MD	1,492	96.4	831	96.7
US trained				
No	575	37.2	312	36.3
Yes	972	62.8	547	63.7
Date of graduation				
< 1975	291	18.8	129	15.0
≥ 1975	1,256	81.2	730	85.0
Type of practice				
Nonprivate	439	28.4	282	32.8
Private	1,108	71.6	577	67.2
No. of patients in cohort†				
1	587	37.9	409	47.6
≥ 2	960	62.1	450	52.4
Chemotherapy‡				
None	746	48.2	424	49.4
Oxaliplatin	432	27.9	289	33.6
Fluorouracil	755	48.8	385	44.8
Irinotecan	NA	NA	194	22.6
Bevacizumab	54	3.5	310	36.1

Abbreviations: DO, doctor of osteopathy; MD, medical doctor; NA, not applicable; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results; SES, socioeconomic status.

* Patients > 65 years of age diagnosed with histologically confirmed colon cancer in the SEER-Medicare database who saw an oncologist between September 1, 2004, and December 31, 2005; for patients with stage IV disease, between January 1, 2005, and December 31, 2005.

† No. of patients in the cohort treated by their primary oncologists.

‡ Not mutually exclusive.

in our stage IV cohort, 859 (76.8%) had a claim submitted by an oncologist. Table 1 lists the characteristics of the patients in each of our cohorts. Patients with stage III disease had a mean age of 77.5 years, were predominantly white (84.0%), lived in urban areas (88.9%), and had no comorbidities (55.1%). Patients with stage IV disease had a mean age of 77.2 years and were also predominantly white (82.4%), lived in urban areas (90.6%), and had no comorbidities (56.2%). There was variability with regard to SES, marital status, and tumor grade. The oncologists for our stage III cohort predominantly were male (79.6%), were MDs (96.4%), had trained in the United States (62.8%), and worked in private practice (71.6%), and the majority had treated two or more patients in the cohort (62.1%). The oncologists for our stage IV cohort predominantly were male (78.7%), were MDs (96.7%), had trained in the United States (63.7%), and worked in private practice (67.2%), and the majority had treated two or more patients in the cohort (52.4%).

Among the 1,547 patients with stage III disease who saw an oncologist, 801 (51.8%) received adjuvant chemotherapy, and

Table 2. Multivariate Analysis of Predictors of Multiagent Chemotherapy Receipt by Patient/Oncologist Characteristics for Oxaliplatin Use (and/or irinotecan use for stage IV)*

Characteristic	Stage III (n = 1,178)† OR	Stage III (n = 1,178)† 95% CI	Stage IV (n = 781)† OR	Stage IV (n = 781)† 95% CI
Patient				
Total patients				
No.		432		357
%		36.7		45.7
Age at diagnosis, years				
65-69		Referent		Referent
70-74	0.49	0.32 to 0.76	0.69	0.41 to 1.16
75-79	0.27	0.18 to 0.42	0.54	0.33 to 0.91
80-84	0.07	0.04 to 0.11	0.21	0.12 to 0.35
≥ 85	0.0045	0.001 to 0.01	0.03	0.01 to 0.08
Sex				
Male		Referent		Referent
Female	0.80	0.58 to 1.10	0.70	0.49 to 1.01
Race				
White		Referent		Referent
Black	0.51	0.28 to 0.94	1.01	0.52 to 1.96
Hispanic	0.23	0.02 to 2.46	1.36	0.43 to 4.26
Other	0.55	0.30 to 1.03	1.07	0.47 to 2.46
Marital status				
Married		Referent		Referent
Single/divorced	0.45	0.32 to 0.62	0.51	0.35 to 0.73
Unknown	0.52	0.26 to 1.04	0.63	0.26 to 1.52
Urban/rural location				
Urban	2.27	1.31 to 3.93	0.62	0.34 to 1.14
SES, quintile				
Lowest		Referent		Referent
Second	0.71	0.41 to 1.25	0.73	0.35 to 1.50
Third	0.68	0.38 to 1.20	1.00	0.48 to 2.09
Fourth	0.99	0.57 to 1.73	0.93	0.44 to 1.96
Highest	0.89	0.50 to 1.57	1.09	0.51 to 2.33
Clinical				
Grade				
Well differentiated		Referent		Referent
Moderately differentiated	2.40	1.25 to 4.58	0.83	0.30 to 2.33
Poorly differentiated	2.74	1.40 to 5.39	0.72	0.25 to 2.08
Undifferentiated	1.29	0.41 to 4.06	0.28	0.06 to 1.37
Unknown	1.29	0.39 to 4.30	0.34	0.12 to 0.99
No. of comorbidities				
0		Referent		Referent
1	0.55	0.40 to 0.78	0.66	0.45 to 0.98
≥ 2	0.36	0.23 to 0.58	0.49	0.29 to 0.81
Hypertension				
No		Referent		Referent
Yes	1.09	0.78 to 1.51	0.95	0.65 to 1.40
Oncologist				
Sex				
Male		Referent		Referent
Female	1.08	0.75 to 1.55	1.04	0.68 to 1.59
US trained				
No		Referent		Referent
Yes	0.75	0.55 to 1.05	1.45	1.02 to 2.06
Date of graduation				
< 1975		Referent		Referent
≥ 1975	1.65	1.11 to 2.45	2.43	1.47 to 4.01
Type of practice				
Nonprivate		Referent		Referent
Private	1.30	0.92 to 1.84	0.88	0.60 to 1.28
No. of patients in cohort				
1		Referent		Referent
≥ 2	1.13	0.83 to 1.55	1.60	1.14 to 2.25

Abbreviations: OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results; SES, socioeconomic status.

* Patients > 65 years of age diagnosed with histologically confirmed colon cancer in the SEER-Medicare database who saw an oncologist between September 1, 2004, and December 31, 2005; for patients with stage IV disease, between January 1, 2005, and December 31, 2005.

† Comparison for patients with stage III disease is between patients who received oxaliplatin and those who received no chemotherapy; comparison for patients with stage IV/recurrent disease is between those who received either oxaliplatin and/or irinotecan and those who received no chemotherapy.

of those, 432 (54.1%) received oxaliplatin. Notably, 54 (6.7%) received adjuvant bevacizumab off label.

Among the 859 patients with stage IV disease who saw an oncologist, 435 (50.6%) received any chemotherapy, and of those, 289 (66.4%) received oxaliplatin, 194 (44.6%) received irinotecan, and 357 (82.1%) received oxaliplatin and/or irinotecan. Among patients with stage IV disease, 310 (71.3%) received chemotherapy as well as bevacizumab.

Predictors of Multiagent Chemotherapy

All multivariate analyses were performed in the group of patients who saw an oncologist. Oncologist characteristics that were analyzed based on the variables in the AMA master file included oncologist, sex, year of graduation (< 1975 or ≥ 1975), primary employment setting (private *v* other), location of training (United States *v* other), and type of degree (MD or DO). Predictors of chemotherapy with oxaliplatin in stage III and chemotherapy with either oxaliplatin and/or irinotecan in stage IV disease relative to no chemotherapy are listed in Table 2. For

Table 3. Multivariate Analysis Predictors of Bevacizumab Receipt by Patient/Oncologist Characteristics*

Characteristic	Stage IV (n = 435)† OR	95% CI
Patient		
Total patients		
No.		310
%		71.3
Age at diagnosis, years		
65-69		Referent
70-74	0.78	0.41 to 1.51
75-79	0.60	0.32 to 1.14
80-84	0.47	0.22 to 1.01
≥ 85	0.35	0.12 to 1.02
Sex		
Male		Referent
Female	1.56	0.95 to 2.56
Race		
White		Referent
Black	0.71	0.29 to 1.70
Hispanic	0.66	0.14 to 3.12
Other	0.69	0.26 to 1.84
Marital status		
Married		Referent
Single/divorced	1.04	0.63 to 1.72
Unknown	2.44	0.36 to 16.73
Urban/rural location		
Urban	0.75	0.34 to 1.66
SES, quintile		
Lowest		Referent
Second	1.98	0.78 to 5.05
Third	1.23	0.50 to 3.01
Fourth	1.24	0.48 to 3.26
Highest	2.30	0.86 to 6.18
Clinical		
Grade		
Well differentiated		Referent
Moderately differentiated	1.61	0.52 to 4.98
Poorly differentiated	1.19	0.37 to 3.85
Undifferentiated	0.37	0.05 to 2.51
Unknown	1.92	0.52 to 7.14
No. of comorbidities		
0		Referent
1	0.43	0.26 to 0.71
≥ 2	0.71	0.32 to 1.59
Hypertension		
No		Referent
Yes	0.89	0.55 to 1.46
Oncologist		
Sex		
Male		Referent
Female	0.53	0.32 to 0.88
US trained		
No		Referent
Yes	1.08	0.65 to 1.78
Date of graduation		
< 1975		Referent
≥ 1975	1.77	0.84 to 3.72
Type of practice		
Nonprivate		Referent
Private	0.96	0.59 to 1.55
No. of patients in cohort		
1		Referent
≥ 2	1.61	1.02 to 2.54

Continued on next column

Abbreviations: OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results; SES, socioeconomic status.

* Patients > 65 years of age diagnosed with histologically confirmed colon cancer in the SEER-Medicare database who saw an oncologist between September 1, 2004, and December 31, 2005; for patients with stage IV disease, between January 1, 2005 and December 31, 2005.

patients with stage III disease, younger age, being married, urban (*v* rural) location, moderately or poorly differentiated tumors, and having a comorbidity score of 0 were associated with receipt of adjuvant oxaliplatin. Black race (OR, 0.51; 95% CI, 0.28 to 0.94) was associated with nonreceipt of adjuvant oxaliplatin. Having an oncologist who graduated medical school after 1975 (OR, 1.65; 95% CI, 1.11 to 2.45) was associated with increased likelihood of receiving adjuvant oxaliplatin.

For patients with stage IV disease, younger age, being married, having a comorbidity score of 0, and having a US-trained oncologist (OR, 1.45; 95% CI, 1.02 to 2.06), an oncologist who graduated after 1975 (OR, 2.43; 95% CI, 1.47 to 4.01), and an oncologist who saw more than one patient in the cohort (OR, 1.60; 95% CI, 1.14 to 2.25) were all associated with receipt of oxaliplatin and/or irinotecan.

Predictors of Bevacizumab

To determine factors associated with the use of bevacizumab beyond the predictors of chemotherapy, we compared patients with stage IV disease who received chemotherapy with bevacizumab with those who received chemotherapy without bevacizumab (Table 3). Among patients with stage IV disease who received chemotherapy, bevacizumab receipt was associated with a comorbidity score of 0, having a male oncologist, and having an oncologist who saw two or more patients in the cohort. None of the factors we examined were associated with receipt of bevacizumab for patients with stage III disease (data not shown).

Further Selection of Patients More Likely to Be Chemotherapy Candidates

In an effort to further characterize patients most likely to be candidates for chemotherapy, we created subgroups of patients

with stage III and IV disease between the ages of 65 and 74 years who had comorbidity scores of 0. In the stage III cohort, we identified 322 patients age 65 to 74 years with comorbidity scores of 0 who saw an oncologist. Of these, 183 received oxaliplatin (56.8%), 75 received FU (23.3%), and 64 received no chemotherapy (19.9%). Of the 1,225 patients with stage III disease who saw an oncologist and were either older than 75 years of age and/or had comorbidity scores greater than 0, 249 (20.3%) received oxaliplatin ($P < .001$). The small number of patients in the group younger than age 75 years with comorbidity scores of 0 precludes multivariable analyses. We repeated a similar analysis for patients with stage IV disease and identified 231 patients between the ages of 65 and 74 years with comorbidity scores of 0, and of those, 134 received multiagent chemotherapy (58.0%). Among the 888 patients who were older than 74 years of age and/or had comorbidity scores greater than 0, 227 received multiagent chemotherapy (25.6%; $P < .001$).

Discussion

Oxaliplatin and bevacizumab were approved for treatment of colon cancer in 2004. We found that in an older population-based sample of patients with colon cancer who were seen by an oncologist and treated in 2005 and 2006, the majority of those who received chemotherapy for stages III (54.1%) and IV disease (66.4%) received oxaliplatin, confirming the rapid and extensive uptake of oxaliplatin in the year after approval. Similarly, more than 70% of patients who received chemotherapy for metastatic colon cancer in 2005 and 2006 in our cohort also received bevacizumab. Use of oxaliplatin for resected and metastatic colon cancers and bevacizumab for metastatic colon cancer is in accordance with evidence-based expert recommendations from 2005.[16,17] Interestingly, 6.7% of patients with stage III disease who received adjuvant chemotherapy also received bevacizumab off label, despite lack of support for its use in that setting.

We investigated what predicted use of these new therapies and found that the patient and tumor characteristics associated with receipt of adjuvant oxaliplatin, including younger age, being married, moderately or poorly differentiated tumors, and having a comorbidity score of 0, were consistent with previous work by our group.[18-20] Higher-grade tumors are associated with increased relapse risk, and fewer comorbidites are associated with better chemotherapy tolerance.[21] These considerations logically factor into the risk/benefit analysis of any decision regarding chemotherapy. Marital status also consistently predicts increased therapy use and may serve as a marker of increased social support.[22] Racial/ethnic disparities in cancer care have been repeatedly reported by our group and others, and black patients in our study were 50% less likely to receive adjuvant oxaliplatin-containing chemotherapy (OR, 0.51; 95% CI, 0.28 to 0.94).[19,23]

Published examinations of the speed and extent of oncology practice changes in population-based samples are limited, but they do suggest that adoption of new therapy can be rapid for one subset of patients and significantly delayed for other groups.[24-26] One recent study compared use of adjuvant chemotherapy for lung cancer in the years 2001 to 2003 with use in 2004 to 2005.[27] The study found that use of adjuvant chemotherapy increased from 7% to 31%, and 4-year overall mortality decreased over the interval. Despite significant research documenting the efficacy of adjuvant colon cancer chemotherapy for node-positive patients, including the use of FU plus leucovorin, overall use in the Medicare population has hovered around 50% for years. Interestingly, the introduction of new drugs, such as oxaliplatin, does not necessarily increase the overall use of adjuvant chemotherapy but instead leads to substitution of the new regimen for the old regimen. A similar pattern was observed in the Ontario Cancer Registry study, which showed that although the use of adjuvant chemotherapy for lung cancer remained low, newly approved drugs were rapidly incorporated into the regimens.

Little research has explored physician characteristics associated with treatment decisions. Previous work on associations between physician characteristics and treatment choices has focused predominantly on surgical therapy and outcomes. Higher surgeon case load has repeatedly been associated with improved surgical outcomes.[28,29] Subspecialty surgical training was also associated with surgical outcomes in one study.[30] In the current study, we found a consistent association between provider volume and use of newer chemotherapy drugs. Having a provider who saw more patients in our cohort was associated with receipt of adjuvant oxaliplatin and bevacizumab for metastatic disease. Our investigation also found that provider medical school graduation after 1975 was associated with use of new therapies.

Our group previously found that women age 65 years and older diagnosed with localized breast cancer were 40% more likely to receive adjuvant chemotherapy if they were seen by oncologists in private practice and 10% more likely if seen by oncologists who graduated after 1975.[31] In our current study, we did not find an association of private practice with oxaliplatin use, but graduation after 1975 was associated with adjuvant oxaliplatin and multiagent chemotherapy for metastatic disease.

We found that 6.7% of patients with stage III disease treated with adjuvant chemotherapy in 2005 received bevacizumab off label; we found no significant predictors of bevacizumab use. There were no randomized trial data in support of bevacizumab use for resected colon cancer in 2005, despite evidence of efficacy for patients with metastatic disease.[4] This off-label use was recently addressed in a randomized phase III trial.[5] In that study, adjuvant bevacizumab provided no benefit over oxaliplatin-containing chemotherapy, and it had additional toxicity. This provides a caution to use of expensive agents off label in the absence of evidence of a benefit. Few published data are available on off-label use of medications in oncology. An article in 1991 analyzed surveys by 681 American Society of Clinical Oncology members and found that 33.2% of all medications were prescribed for off-label use; 56.0% of patients received at least one medication for an off-label use.[32] Several other studies have confirmed widespread off-label medication use in oncology.[33,34] Although off-label use may often be related to delayed

regulatory approval for uses supported by data, our observation of adjuvant bevacizumab use in patients with localized colorectal cancer likely represents inappropriate use. Adjuvant bevacizumab in 2005 and 2006 had financial costs and likely caused adverse effects for patients.

Our study had several limitations. First, our short treatment interval (1 year after most recent diagnoses) limited the power of some analyses to detect associations between provider characteristics and new therapies. The relatively small number of patients treated with bevacizumab makes subgroup analyses to detect heterogeneity of treatment patterns difficult. Second, as with all retrospective analyses, there may be unmeasured confounders that limit our ability to draw meaningful relationships between provider characteristics and use of current therapies. Third, regarding the off-label use of bevacizumab for patients with stage III cancer, it is likely that there is some degree of stage misclassification and/or stage change within a short interval after stage data are submitted to SEER. It is possible that patients classified as having stage III disesae truly had stage IV disease and received bevacizumab in accordance with evidence-based guidelines. Regarding the limitations of using Medicare data, the use of capecitabine as a substitute fluoropyrimidine in place of FU was approved by the FDA in June 2005 for both adjuvant and metastatic colon cancers. Medicare does not record oral medications, and hence, there may be an estimated 10% to 15% of patients who received this form of therapy. Our Medicare data set also only covered patients age 65 years or older and cannot be assumed to represent national treatment patterns in younger patients. Finally, there are many factors that contribute to decisions regarding use of new therapy, including oncologists' previous chemotherapy experience, perception of benefit, and interactions with industry and other physicians, which cannot be examined in our data set.[26]

We found rapid uptake of bevacizumab and oxaliplatin for colon cancer therapy, but significant differences related to patient and provider characteristics existed. Deeper understanding of the factors associated with therapy provides a necessary foundation for attempts to broaden access to evidence-based cancer care.

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