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DETERMINANTS OF ADJUVANT OXALIPLATIN RECEIPT AMONG OLDER STAGE II AND III COLORECTAL CANCER PATIENTS

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Abstract

Purpose—Controversy exists regarding adjuvant oxaliplatin treatment among older stage II and III colorectal cancer (CRC) patients. We sought to identify patient/tumor, physician, hospital, and geographic factors associated with oxaliplatin use among older patients.

Methods—Individuals diagnosed at age>65 with stage II/III CRC from 2004–2007 undergoing surgical resection and receiving adjuvant chemotherapy were identified using the Surveillance, Epidemiology and End Results program (SEER)-Medicare, a database including patient/tumor and hospital characteristics. Physician information was obtained from the American Medical Association. We used Poisson regression to identify independent predictors of oxaliplatin receipt. The discriminatory ability of each category of characteristics to predict oxaliplatin receipt was assessed by comparing the area under the receiver operating curve (AUC) from logistic regression models.

Results—We identified 4,388 individuals who underwent surgical resection at 773 hospitals and received chemotherapy from 1,517 physicians. Adjuvant oxaliplatin use was higher among stage III (colon=56%, rectum=51%) compared to stage II patients (colon=37%, rectum=35%). Overall, patients who were older, diagnosed before 2006, separated, divorced or widowed, living in a higher poverty census tract or in the East or Midwest, or with higher levels of comorbidity were less likely to receive oxaliplatin. Patient factors and calendar year accounted for most of the variation in oxaliplatin receipt (AUC=75.8%).

Conclusion—Adjuvant oxaliplatin use increased rapidly from 2004–2007 despite uncertainties regarding its effectiveness in older patients. Physician and hospital characteristics had little influence on adjuvant oxaliplatin receipt among older patients.

Keywords

colorectal cancer; chemotherapy; SEER Program; Medicare

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INTRODUCTION

In 2011, an estimated 141,210 patients were diagnosed with colorectal cancer (CRC) in the United States (US), with 49,380 deaths.[1] Healthcare spending for CRC was estimated at $14.1 billion in 2010.[2, 3] As the median age at CRC diagnosis is 69 years, older patients account for a substantial portion of the overall CRC disease burden in the US.[4]

Adjuvant chemotherapy after surgical resection improves overall survival among older stage III colon cancer patients. Three adjuvant chemotherapies are available and include 5-fluorouracil (FU), capecitabine, or the combination of 5-FU or capecitabine with oxaliplatin; no other agents have been shown to improve outcomes.[5–8] Adjuvant chemotherapy with 5-FU compared to surgery alone reduces the risk of death by 24% among older stage III colon cancer patients.[9] Randomized controlled trials (RCTs) demonstrated that adding adjuvant oxaliplatin to 5-FU leads to an incremental 4.2% reduction in death among patients with stage III colon cancer.[10–13] However, individuals enrolled in these RCTs had a median age at diagnosis of 60–63 years, and only 17% were ≥70 years,[14] limiting the generalizability of these findings to older patients. Recent studies[15–21] have shown that the addition of adjuvant oxaliplatin to 5-FU or capecitabine results in minimal, if any incremental survival benefit for older stage III colon cancer patients and average risk stage II colon cancer patients. Based upon these findings, the National Comprehensive Cancer Network (NCCN) guidelines now state that there is no demonstrated benefit to the addition of adjuvant oxaliplatin to 5-FU in average-risk stage II colon cancer or in patients >70 years.[22] The role of adjuvant oxaliplatin in rectal cancer is not yet defined.

In light of the growing concerns regarding the incremental benefits of oxaliplatin in addition to 5-FU in these subgroups and the lack of RCT evidence regarding its role in rectal cancer, we sought to examine the dissemination of adjuvant oxaliplatin among older patients and factors influencing its use in routine clinical practice.”

METHODS

Data sources

The SEER-Medicare database is a linkage of two large population-based data sources providing detailed clinical and healthcare utilization information on Medicare beneficiaries diagnosed with cancer.[23] The SEER registries collect demographic, clinical and tumor characteristics, vital status, and cause of death for all incident cancers reported for individuals residing within one of the registry areas, covering approximately 28% of the US.[24] Patients in SEER are linked to their Medicare Part A and B claims.[25] Nearly all Medicare beneficiaries are eligible for Part A and almost 93% opt to enroll in the Part B.[26] The SEER-Medicare Hospital file reports descriptive information for hospitals that are part of the SEER-Medicare database,[27] including whether hospitals were NCI-designated cancer centers or participated in cooperative groups for clinical trials. Medicare claims were linked to the Hospital file using a unique number. The AMA Physician Masterfile data contain information on the characteristics of >1 million physicians in the US which are linked to Medicare claims by each physician’s Unique Physician Identification Numbers (UPINs).[28–30]

Study Cohort

We identified all patients in the SEER data diagnosed at age >65 with their first primary stage II or III cancer of the colon or rectum.[31] Exclusions included: diagnoses at autopsy or death; a missing month of diagnosis; those without continuous Medicare Part A and B fee-for-service enrollment for the 12-months before and 8-months after diagnosis (as healthcare utilization and treatment information would not be complete for all patients).

To identify characteristics of the hospital where cancer surgery was performed, we restricted this cohort to individuals with a surgical claim (i.e., colectomy or proctectomy) in the 6-months following diagnosis. If a patient had surgical claims from multiple hospitals, the first hospital was retained for analysis. We linked the cohort to the SEER-Medicare Hospital file by the provider number and year of diagnosis for each patient. Hospitals that did not match were excluded.

To examine characteristics of physicians providing chemotherapy, eligible patients had to have at least one claim for a specific chemotherapeutic agent during the initial chemotherapy treatment period (described below). The physician with the most chemotherapy-related claims during the initial chemotherapy treatment period was considered the treating physician.[32] UPINs that did not match to the AMA Physician Masterfile were excluded.

Measurement of adjuvant oxaliplatin

We categorized patients as receiving adjuvant chemotherapy with oxaliplatin or without oxaliplatin using the algorithm in Figure 1. Because adjuvant chemoradiotherapy for rectal cancer may be delivered pre- or post-operatively, a different exposure window was required for patients receiving post-operative adjuvant radiotherapy to distinguish between radiosensitizing chemotherapy and systemic adjuvant chemotherapy. We defined adjuvant chemotherapy using a 120-day window to avoid misclassifying chemotherapy for recurrent cancer as adjuvant therapy. Patients were divided into an oxaliplatin group, those having ≥1 claim for oxaliplatin within 60 days from the first chemotherapy claim, and a non-oxaliplatin group, those without any oxaliplatin claims within 60 days from the first chemotherapy. The validity of Medicare claims to identify chemotherapy administration and oxaliplatin has been previously reported to be high.[33, 34]

Patient characteristics

Characteristics including year of diagnosis, sex, age at diagnosis (66–69, 70–74, 75–79, 80–84, or 85+), race/ethnicity (White Non-Hispanic, Black Non-Hispanic, Other Non-Hispanic, Hispanic, or Unknown), marital status (married, single, other (divorced, separated, widowed), or unknown), and region of residence (Northeast, South, Midwest, or West) came from SEER. County-level metropolitan area was defined as metropolitan or non-metropolitan. Census tract level information about the percentage of residents living below the federal poverty level served as an aggregate measure of socioeconomic status and was categorized into quartiles: ≤4%, 4.01–≤8%, 8.01–≤15%, and >15, as the census tract poverty variable may be the best proxy measure of SES for elderly Medicare beneficiaries.[35, 36] Each patient's pre-existing health conditions in the 365 days pre-diagnosis were measured using the Klabunde adaptation of the Charlson Comorbidity Index (CCI).[37]

Hospital and physician characteristics

Hospital characteristics included NCI center designation (none, clinical, or comprehensive), NCI cooperative membership group count (0 or ≥1), teaching hospital status (yes/no), type of hospital (non-profit, private, or government), and total bed size, measured in quartiles (<204, 204–343, 344–487, or 488+). Physician characteristics included medical degree (Medical Doctor (MD) or Doctor of Osteopathy (DO)), whether the physician was trained in the US (yes/no), year of medical school graduation (<1981 or ≥1981), primary specialty (oncology, hematology/oncology, hematology, internal medicine, or other), and sex.

Statistical analysis

We estimated the proportion of patients receiving adjuvant oxaliplatin by year, cancer site, and stage. Bivariable prevalence ratios (PRs) for the receipt of oxaliplatin were calculated

for each multilevel characteristic. Patient observations were clustered within hospitals and physicians in a non-nested manner. Our analysis accounted for this correlation and produced estimates of marginal (population-averaged) associations.[38] We estimated adjusted PRs (aPRs) for all variables using multivariable Poisson models with a log link and generalized estimating equations with an independent working correlation matrix. Stratified analyses for colon and rectal cancer were performed. Finally, we assessed the discriminatory ability of a variety of logistic regression models to determine adjuvant oxaliplatin receipt by comparing the area under the receiver operating curve (AUC). Models included combinations of calendar year and patient/tumor, physician, hospital, and geographic characteristics. All analyses were conducted using the SAS Version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

We identified 4,388 patients diagnosed with stage II or III CRC who received chemotherapy and met all eligibility criteria for inclusion (Figure 2). The study population was primarily over the age of 70 at diagnosis (73%), White Non-Hispanic (81%), married (61%), living in a metropolitan area (84%), and free from comorbidities (68%). Most tumors were located in the colon (85%) and diagnosed at stage III (74%) (Table 1).

The majority of the 1,517 physicians were male (81%), MDs (97%), US-trained (67%), medical school graduates ≥1981 (56%) with a primary specialty of oncology or hematology/oncology (76%) (Table 2). Three percent of the 773 hospitals had a NCI clinical or comprehensive cancer center designation and 48% had at least one cooperative group membership. Almost 40% were teaching hospitals and 62% were non-profit entities.

The prevalence of adjuvant oxaliplatin treatment over the 4-year study period was 52% and 46% for patients diagnosed with colon and rectal cancer, respectively. There was a steady increase in the prevalence of adjuvant oxaliplatin use over time which was similar for all site and stage subgroups (Figure 3). By 2007, 60% and 73% of stage II and III colon and 52% and 68% of stage II and III rectal cancer patients received oxaliplatin, respectively.

Patients diagnosed in earlier years were less likely to receive adjuvant oxaliplatin than those diagnosed in 2007 (e.g., 2004: aPR=0.42, 95% CI: (0.37, 0.47), Figure 4). Patients with colon vs. rectal cancer were more likely to receive oxaliplatin (aPR=1.15, 95% CI: (1.05, 1.26)), whereas those with stage II vs. III disease were less likely (aPR= 0.65, 95% CI: (0.60, 0.71)). Increasing age was associated with a gradual monotonic decrease in the likelihood of oxaliplatin receipt (e.g., 85+ vs. 66–69: aPR =0.22, 95% CI: (0.14, 0.34)) and patients with increased comorbidities were less likely to receive oxaliplatin compared to those with no comorbidity (e.g., Charlson Score of 1 vs. 0: aPR= 0.92, 95% CI: (0.87, 0.98). Additionally, patients who were separated, divorced or widowed (vs. married), living in the East or Midwest (vs. West), residing in a non-metropolitan area (vs. metropolitan area) or in a census tract with a higher proportion of individuals living under the poverty level were less likely to receive oxaliplatin. No physician- or hospital-level variables were strongly associated with adjuvant oxaliplatin receipt in the overall analysis. Results from the cancer site-stratified analyses were similar, although less precise for rectal cancer due the smaller number of patients (data not shown). Two exceptions were that among rectal cancer patients, surgical treatment at an NCI comprehensive cancer center was associated with increased adjuvant oxaliplatin use (aPR=1.48, 95% CI: 1.15, 1.90), while Hispanic ethnicity was associated with decreased use (aPR=0.52, 0.32, 0.86). Among stage II colon cancer patients, more patients with T4 tumors (40%) received oxaliplatin compared to those with T3 tumors (36%).

The category headings in Figure 4 denote the AUC for components of the logistic regression model (calendar year, patient/tumor, physician, hospital, and geographic). The AUC reports the ability of each model to accurately distinguish between those patients who received adjuvant oxaliplatin and those who did not. When calendar year was included alone, the model had fair ability to discriminate oxaliplatin users (AUC=68%). The addition of patient/tumor factors enhanced the model's discriminatory ability (AUC=75.8 %). However, when physician, hospital, and geographic factors were added separately to calendar year, the AUC only increased to 68.9%, 68.9%, and 69.1% respectively. The full model AUC was 76.6%; therefore, among patients who received chemotherapy, physician and hospital characteristics contributed very little to the determination of oxaliplatin receipt.

DISCUSSION

This population-based analysis demonstrates substantial increases in oxaliplatin use among older stage II and III CRC patients who received chemotherapy from 2004–2007. By 2007, the prevalence of oxaliplatin treatment was 60% and 73% among stage II and III colon cancer patients and 52% and 68% among stage II and III rectal cancer patients, respectively. Patient- and tumor-level characteristics, together with calendar year, accounted for most of the discriminatory power in determining oxaliplatin use in older CRC patients, while physician and hospital characteristics contributed little.

Patients treated by providers within the Community Clinical Oncology Program (CCOP), a network connecting NCI cooperative groups to community physicians treating cancer patients, were recently found to be more likely than those who did not to receive adjuvant oxaliplatin.[39] CCOP data was not available for our analysis; however, when restricted to stage III colon cancer patients, we did not find an association between hospital cooperative group participation and adjuvant oxaliplatin use (aPR=0.98, 95% CI: 0.91, 1.05). This discrepancy may reflect that our study examined a slightly later time period, potentially weakening the impact of cooperative group membership on oxaliplatin diffusion. By 2007, 73% of all older stage III colon cancer patients in our study received adjuvant chemotherapy with oxaliplatin, suggesting that its adoption in routine practice was rapid and widespread across all physicians. However, our finding that rectal cancer patients undergoing surgery at an NCI comprehensive cancer centers were more likely to receive adjuvant oxaliplatin compared with similar patients at hospitals without an NCI designation may be due to the unique timing and coordination of surgery, radiation, and chemotherapy required for rectal cancer treatment. The sex and race/ethnicity of patients were not predictive of adjuvant oxaliplatin receipt, which may reflect the uniform insurance setting of our study limiting variations in access to care.

Among patient subgroups where RCT evidence is entirely lacking (i.e., stage II and III rectal cancer) or has shown no benefit (i.e., stage II colon cancer),[11] we found widespread adjuvant oxaliplatin use by 2007 in older CRC patients. Well over half of all stage II colon and stage II and III rectal cancer patients undergoing adjuvant chemotherapy received oxaliplatin as part of their adjuvant chemotherapy. Rectal cancer patients have not been included in RCTs examining adjuvant oxaliplatin and as such, there is no phase III evidence supporting its use. It is possible that higher local and systemic recurrence rates lead physicians and older patients to choose adjuvant oxaliplatin treatment;[40, 41] however, the added toxicity of (neo)adjuvant radiotherapy makes tolerance of adjuvant chemotherapy more challenging. Whether this practice is appropriate will hopefully be answered by ongoing trials examining the role of oxaliplatin in adjuvant chemotherapy of rectal cancer (PETACC 6 and German Rectal Cancer Study Group CAO/ ARO/AIO-04). However, these trials are unlikely to include adequate numbers of older rectal cancer patients for sub-analysis, and therefore some uncertainty will remain.

Even in colon cancer, the evidence to support the addition of adjuvant oxaliplatin to 5-FU in older patients is weak. An initial pooled analysis of four RCTs demonstrated that the efficacy of adding oxaliplatin to 5-FU was similar in older and younger patients with stage III and metastatic CRC.[14] However, three recent RCT analyses relying on subgroup or pooled data have reported conflicting results regarding the efficacy of adjuvant oxaliplatin in older patients.[19, 20, 42] Two analyses of multiple observational databases found that the addition of adjuvant oxaliplatin treatment may benefit those younger than 75 years old,[17] but for those ≥80 any benefit is likely modest.[18] Therefore, as controversy remains regarding adjuvant oxaliplatin in older stage III colon cancer patients, any potential benefits must be carefully considered alongside patient preferences and the cost and risk of adverse events.

Our study has multiple strengths. The cohort included a large sample derived from population-based cancer registries linked to longitudinal Medicare claims. These data were augmented by information in the AMA Masterfile and SEER-Medicare Hospital file. The aggregation of data resulted in a rich data source to examine the influence of multilevel characteristics on the receipt of oxaliplatin. Our analysis reflects patterns of chemotherapy use in the community setting.

However, our study is limited by the constraints of the data sources. SEER-Medicare contains information on many patient and tumor characteristics that may be associated with treatment patterns, but unobserved factors such as patient preferences, financial considerations, or functional status may also influence treatment decisions. Further linkage efforts to data sources including electronic medical records or patient surveys may improve measurement of these factors for future research. Because clinical stage was not available in the SEER data, we relied upon pathological staging and as a result may have selected neoadjuvantly-treated rectal cancer patients with a poorer prognosis. Our analysis did not examine within-physician variation in prescribing using a random effects framework, which may further illuminate patterns of physician preference regarding the use of oxaliplatin. Lastly, a number of exclusions were made in the creation of our study population and thus the findings from our analysis may not be generalizable to individuals <66 years or managed care enrollees.

In conclusion, adjuvant oxaliplatin was increasingly used to treat stage II and III CRC patients following its approval in 2004 and its use was influenced strongly by patient, as opposed to physician or hospital, characteristics. By 2007, 70% of all chemotherapy-treated stage II and III CRC patients received adjuvant oxaliplatin, despite no evidence to support its use in rectal cancer, and mounting evidence against its use in stage II and older stage III colon cancer patients. The widespread dissemination of oxaliplatin into the older population highlights the critical importance of studying the benefits of anticancer therapies in older patient populations. Future studies should focus on the comparative effectiveness and safety of adjuvant chemotherapy with oxaliplatin in older stage II and III rectal cancer patients, as utilization within these patient groups were substantial and the evidence for benefit and harm are unknown.

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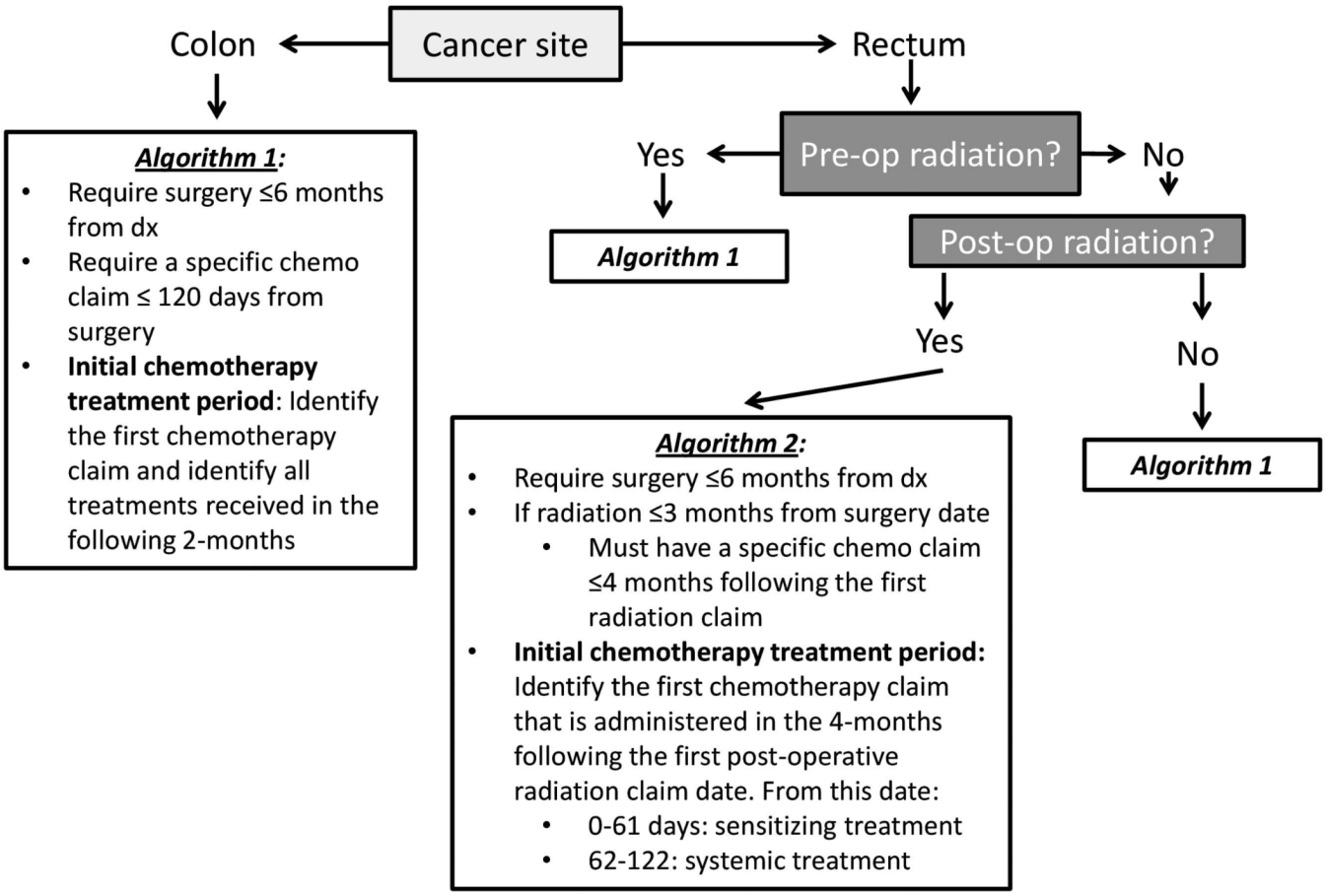

Figure 1. Administrative algorithms used to define adjuvant chemotherapy treatment for stage II and III colorectal cancer patients

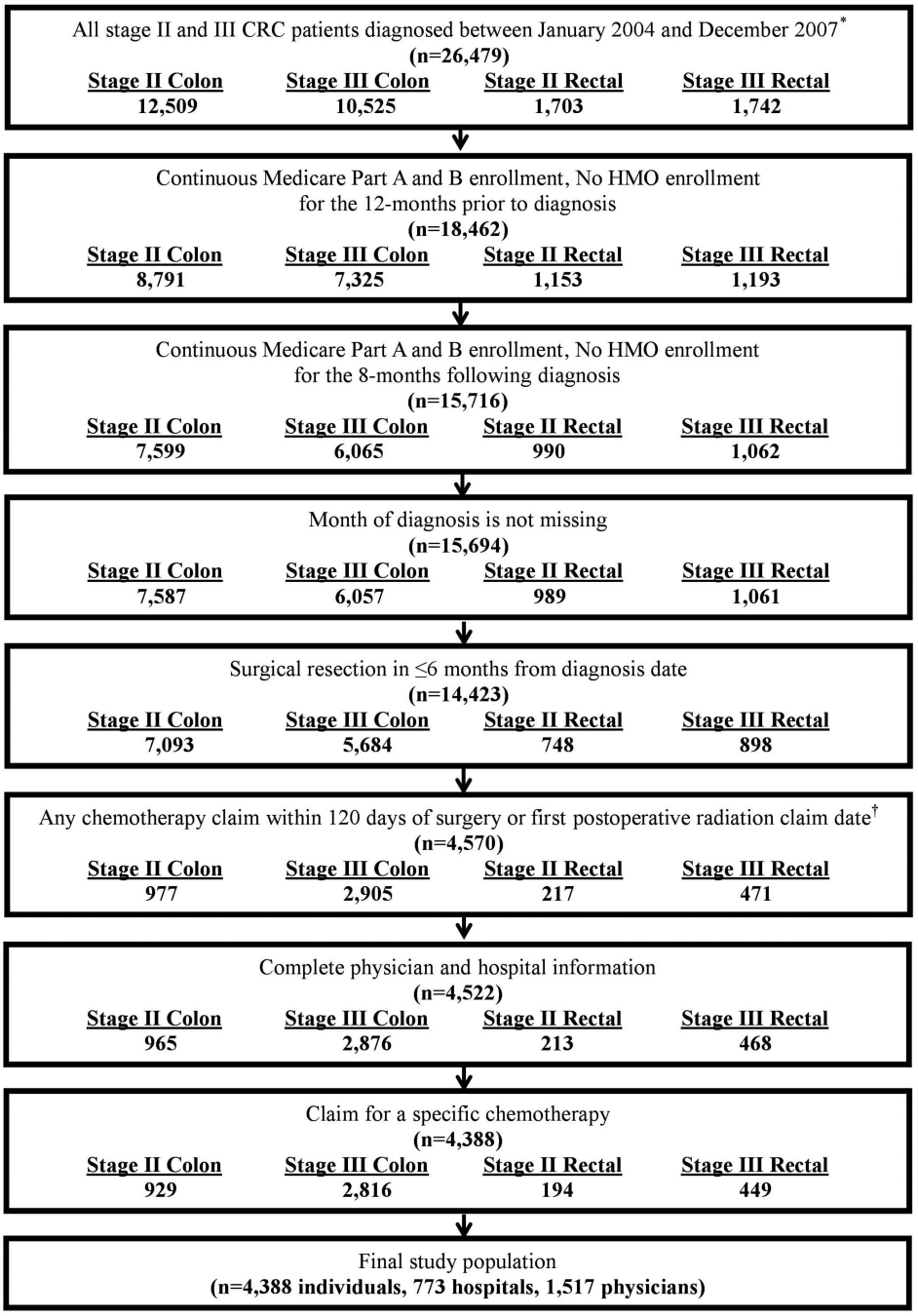

Figure 2. Study population flow chart

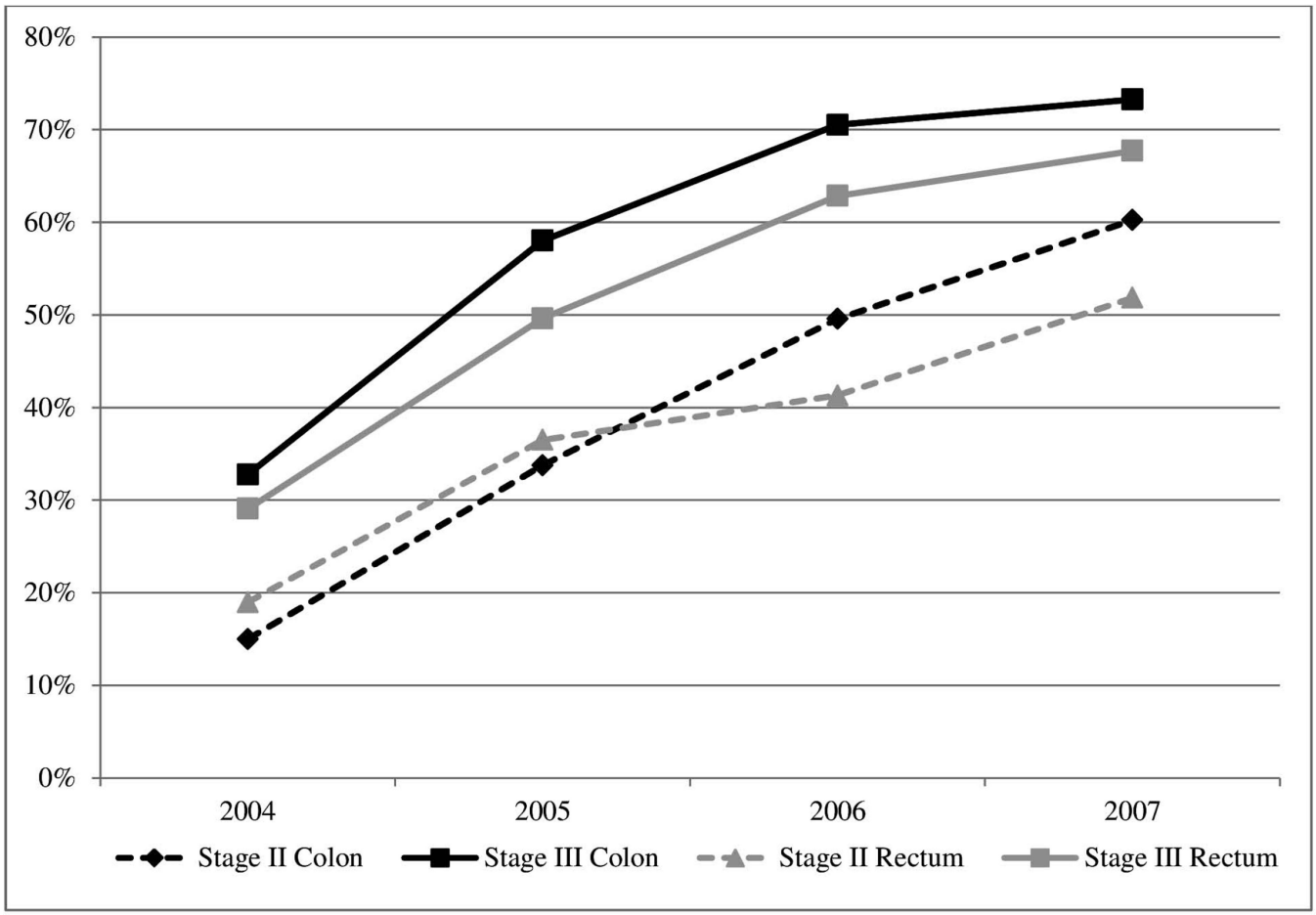

Figure 3. Prevalence of adjuvant oxaliplatin use by cancer site and stage among older colorectal cancer patients who received chemotherapy treatment from 2004–2007

The annual prevalence among stage II and III colon cancer patients is represented by the black dashed and solid line, respectively, and among stage II and III rectal cancer patients by the grey dashed and solid line, respectively. Less than 3% (n=114) of patients received adjuvant irinotecan during the study period.

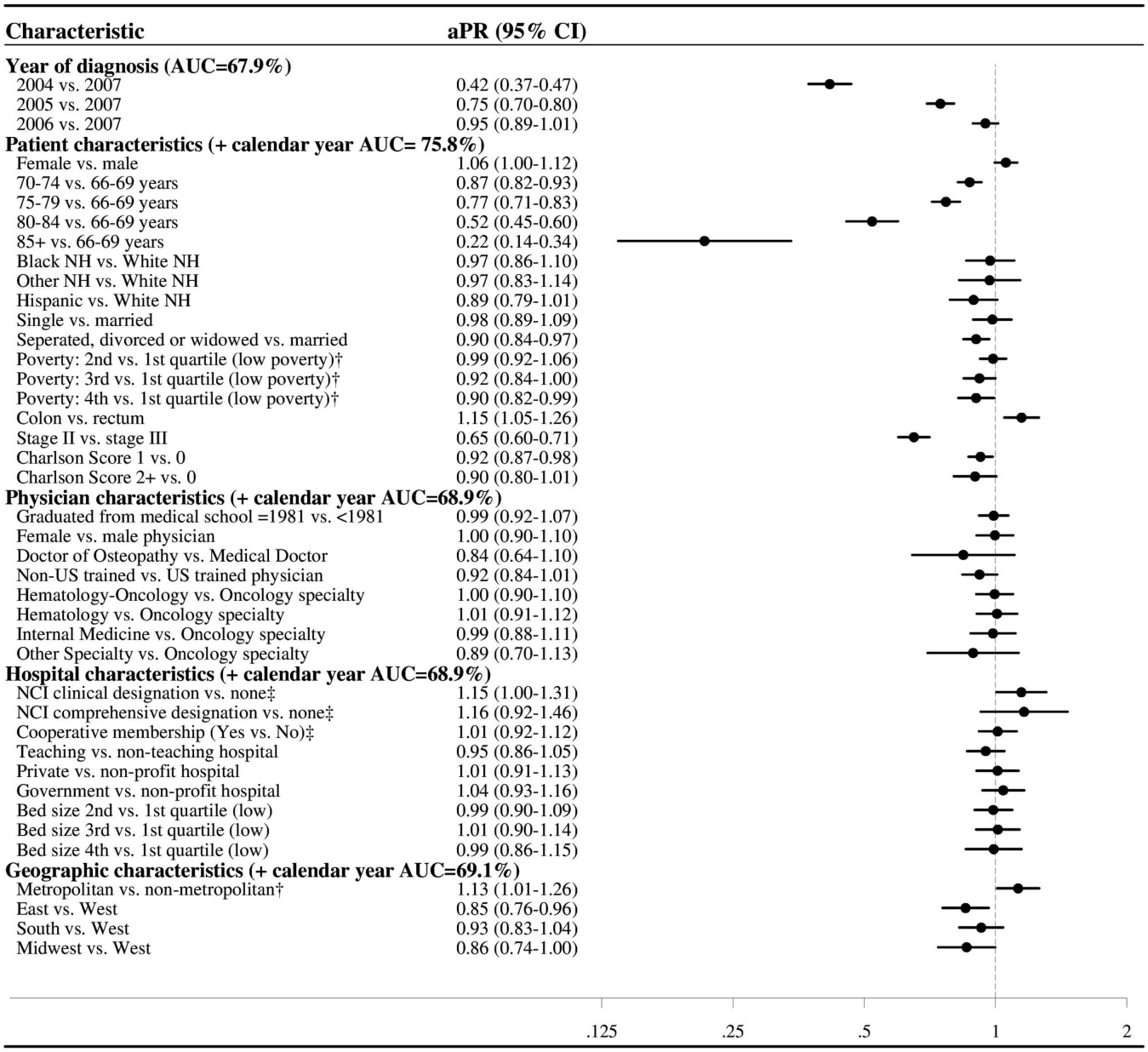

Figure 4. Forest plot summarizing the multivariable adjusted prevalence ratio estimates for the associations between multilevel characteristics and adjuvant oxaliplatin receipt among older stage II and III CRC patients treated with chemotherapy

Table 1

Characteristics of older stage II or III colorectal cancer patients by chemotherapy treatment group*

Patient and geographic characteristics	All stage II and III colorectal cancer patients		Patients receiving chemotherapy treatment: without oxaliplatin†		Patients receiving chemotherapy treatment: with oxaliplatin	
	n=4,388	col %	n=2,145	row %	n=2,243	row %
Demographic characteristics						
Gender						
Male	2,087	48	1,026	49	1061	51
Female	2,301	52	1,119	49	1,182	51
Age at diagnosis (mean, SD)	73.7 (5.3)		74.8 (5.6)		72.6 (4.8)	
65 – 69	1,199	27	456	38	743	62
70 – 74	1,360	31	624	46	736	54
75 – 79	1,144	26	584	51	560	49
80 – 84	563	13	375	67	188	33
85+	122	3	106	87	16	13
Race						
White Non-Hispanic	3,551	81	1,723	49	1,828	51
Black Non-Hispanic	273	6	141	52	132	48
Hispanic	285	6	153	54	132	46
Other Non-Hispanic	271	6	126	46	145	54
Unknown	8	0	2	25	6	75
Marital status						
Married	2,663	61	1,238	46	1,425	54
Single	291	7	136	47	155	53
Separated, widowed, or divorced	1,288	29	705	55	583	45
Unknown	146	3	66	45	80	55
Percentage living below poverty level‡						
≤ 4%	1,052	24	476	45	576	55
4–8%	1,250	28	579	46	671	54

Patient and geographic characteristics	All stage II and III colorectal cancer patients		Patients receiving chemotherapy treatment			
			without oxaliplatin[†]		with oxaliplatin	
8–15%	1,031	23	531	52	500	48
>15%	1,055	24	559	53	496	47
Year of diagnosis						
2004	1,283	29	926	72	357	28
2005	1,157	26	567	49	590	51
2006	987	22	361	37	626	63
2007	961	22	291	30	670	70
Charlson Comorbidity Index						
0	2,982	68	1407	47	1575	53
1	1,029	23	534	52	495	48
2+	377	9	204	54	173	46
Tumor characteristics at diagnosis						
Cancer site						
Colon	3,745	85	1,799	48	1,946	52
Rectum	643	15	346	54	297	46
AJCC/Derived AJCC stage						
II	1,123	26	713	63	410	37
III	3,265	74	1,432	44	1,833	56
Geographic characteristics						
County of residence size (metro area)[‡]						
Metropolitan	3,685	84	1,765	48	1,920	52
Non-metropolitan	703	16	380	54	323	46
Region						
Northeast	1,045	24	544	52	501	48
South	873	20	441	51	432	49
Midwest	716	16	389	54	327	46
West	1,754	40	771	44	983	56

[*] Cases obtained from the Surveillance, Epidemiology and End Results Program 17 registries were included in this analysis.

[†] 94% of the individuals who received treatment without oxaliplatin (n=2,473) received 5-FU or capecitabine alone. All remaining individuals (n=163) received another combination of chemotherapy agents.

[≠] Percentage of census tract living below the poverty line and county of residence in metro area size are linked from 2000 Census data.

Table 2

Characteristics of physicians and hospitals providing care for older stage II and III colorectal cancer patients

Characteristic	Physicians/ hospitals included in analysis		Patients receiving chemotherapy treatment			
			without oxaliplatin *		with oxaliplatin	
	n	col%	n=2,145	row %	n=2,243	row %
Physician characteristics (n=1,517)						
Degree						
MD	1,464	97	2,049	49	2,174	51
DO	53	3	96	58	69	42
US-Trained						
Yes	1,012	67	1,351	47	1,524	53
No	505	33	794	52	719	48
Medical School Graduation						
<1981	666	44	1,025	51	1,001	49
≥1981	851	56	1,120	47	1,242	53
Primary specialty						
Oncology	681	45	1,023	48	1,095	52
Hematology/Oncology	477	31	660	50	673	50
Hematology	160	11	223	48	237	52
Internal Medicine	133	9	188	50	189	50
Other specialty	66	4	51	51	49	49
Gender						
Male	1,235	81	1,832	49	1,925	51
Female	282	19	313	50	318	50
Hospital characteristics (n=773 unique) †						
NCI center designation						
None	802	97	2,091	49	2,158	51
Clinical	4	0	7	39	11	61
Comprehensive	20	2	47	39	74	61
NCI cooperative group membership count						

Characteristic	Physicians/ hospitals included in analysis		Patients receiving chemotherapy treatment			
			without oxaliplatin*		with oxaliplatin	
None	426	52	730	51	709	49
1+	400	48	1,415	48	1,534	52
Teaching hospital						
Yes	319	39	1,153	50	1,142	50
No	502	61	988	47	1,098	53
Unknown	5	1	4	57	3	43
Type of hospital						
Non-profit	512	62	1,693	50	1,706	50
Private	154	19	225	46	259	54
Government	155	19	223	45	275	55
Unknown	5	1	4	57	3	43
Total bed size						
< 204 beds	381	46	550	50	554	50
204 – 343 beds	197	24	531	49	563	51
344 – 487 beds	134	16	521	48	575	52
488+ beds	113	14	543	50	550	50

NCI=National Cancer Institute

*94% of the individuals who received treatment without oxaliplatin (n=2,473) received 5-FU or capecitabine alone. All remaining individuals (n=163) received another combination of chemotherapy agents.

†All hospital information was obtained from the year of patient diagnosis with exception of the NCI cancer center designation and cooperative group count which are reported for the year 2002. The total number of hospitals reported here (n=874) is greater than the total number of unique hospitals because some of the hospital characteristics changed over time and are reported here according to year of the patient's cancer diagnosis.