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Trends in the use of evidence-based therapy for resectable gastric cancer

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Abstract

Background and Objectives—Two pivotal randomized controlled trials (RCTs), the Intergroup (INT-0116) and Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trials, demonstrated a survival benefit of multimodality therapy in patients with resectable gastric cancer. The purpose of this study was to determine utilization rates of these treatment regimens in the U.S. and to identify factors associated with receipt of evidence-based care.

Methods—We performed a retrospective cohort study of patients with Stage IB–Stage IV (M0) gastric adenocarcinoma who underwent resection from 1991–2009 using the linked SEER–Medicare database.

Results—Only 19.1% of patients received post-operative chemoradiation therapy (CRT), and 1.9% received peri-operative chemotherapy; most patients underwent surgery alone (60.9%). Patients with more advanced stage, younger age, and fewer comorbidities were more likely to receive evidence-based care. We found no association between National Cancer Institute (NCI) designation and delivery of multimodality therapy. However, patients who underwent medical oncology consultation were much more likely to receive evidence-based treatment (OR 3.10, 95% CI 2.35–4.09).

Conclusions—Rates of peri-operative chemotherapy and post-operative CRT in patients with resected gastric cancer remain remarkably low, despite high-quality RCT evidence demonstrating their benefit. Furthermore, NCI designation does not appear to be associated with administration of evidence-based treatment.

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Keywords

stomach neoplasms; chemotherapy; adjuvant; chemoradiotherapy; adjuvant; epidemiology

Introduction

Gastric adenocarcinoma is the fourth most common cancer worldwide, with an expected incidence of 989,600 cases in 2008 [1]. Although the majority of cases occur in developing countries, there were an estimated 21,600 new cases and 10,990 deaths from gastric cancer in the U.S. in 2013 [2]. Most patients in the U.S. present with locally advanced cancer extending through the serosa or involving perigastric lymph nodes (LN) [3]. Surgical resection remains the only curative option for gastric adenocarcinoma. However, even after resection, locoregional and systemic recurrence rates remain high, especially in patients presenting with more advanced disease [4]. Given the high rates of locoregional and systemic recurrence after resection, the use of adjuvant chemotherapy and/or radiation therapy has been investigated.

The U.S. Intergroup study (INT-0116) published in 2001, found an improvement in overall survival for patients with Stage IB to IV (M0) gastric cancer who underwent curative resection followed by post-operative 5-fluoruracil (5-FU) chemoradiation therapy (CRT) compared with surgical resection alone [5]. Subsequently in 2006, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial demonstrated an improvement in overall survival for Stage II to Stage IV (M0) patients who received peri-operative chemotherapy with epirubicin, cisplatin, and 5-FU compared with patients who underwent surgery and observation [6]. Currently, both the Intergroup and MAGIC regimens are utilized in the US; however, there have been no direct comparisons between the two approaches.

Despite the randomized, controlled trial (RCT) data demonstrating a benefit of adjuvant therapy, widespread use of either treatment regimen has not been demonstrated in the literature. A recent study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database demonstrated that 30% of eligible Stage IB-Stage IV (M0) patients received post-operative CRT from 2000–2002 [7]. Similarly, based on data from the National Cancer Database (NCDB) from 1998–2005, approximately 60% of patients who underwent gastrectomy for gastric adenocarcinoma did not receive any post-operative multimodality therapy [8]. There is also evidence to suggest that surgical treatment in the U.S. may not be consistent with evidence-based recommendations. A study using SEER-Medicare data demonstrated that despite evidence supporting the benefit of staging laparoscopy in gastric cancer patients, less than 8% undergo the procedure during their clinical course [9].

The etiology of these low utilization rates is unknown. There is evidence to suggest that patients treated at specialty cancer centers such as National Cancer Institute (NCI) designated cancer centers demonstrate better LN clearance and improved survival after gastrectomy; however, it remains unclear whether expert centers are more likely than other

hospitals to administer evidence-based multimodality therapy to gastric cancer patients [10–12].

The primary purpose of this study was to describe the current patterns of care for Stage IB–IV (M0) gastric cancer in the U.S. We sought to determine specific utilization rates of peri-operative chemotherapy and post-operative CRT as well as to evaluate trends in use of these regimens based upon timing of trial publications. Our secondary aim was to determine whether NCI designation status was associated with increased delivery of evidence-based multimodality treatment among patients with resectable gastric cancer. We hypothesized that patients treated at an NCI designated center are more likely to receive evidence-based peri-operative chemotherapy or post-operative CRT than patients treated at other hospitals.

Materials and Methods

Data Sources

We performed a retrospective cohort study of all patients who underwent surgical resection for a new diagnosis of gastric adenocarcinoma between 1991 and 2009 using the most recently available linked SEER-Medicare database, with Medicare follow-up through 2010. The NCI SEER program collects cancer incidence and survival data from cancer registries covering approximately 14% of the U.S. population from 1992–1999, and 28% at present, and is consistent with the overall population in demographics [13]. The SEER-Medicare database links SEER with Medicare claims, including hospital, physician, and outpatient claims for covered health services.

The study protocol was approved by the institutional review board of Vanderbilt University.

Cohort Selection

Patients were included only if age ≥ 66 years to eliminate patients enrolled in Medicare for alternative indications. Patients with Health Maintenance Organization (HMO) coverage were excluded. Continuous Medicare coverage for at least 6 months before and after the date of diagnosis was required in order to adequately assess for comorbidities.

Patients were included only if assigned an ICD-O-3 histology code for gastric adenocarcinoma; all other tumor types were excluded. Only patients with AJCC 6th edition Stage IB through Stage IV (M0) were included. All patients must have undergone surgical resection defined by International Classification of Disease, Ninth Revision (ICD-9) procedure codes for partial or total gastrectomy (Appendix 1). Finally, to limit the cohort to only those patients treated for gastric cancer, patients who received pre-operative CRT or had an ICD-9 procedure code for esophagectomy were excluded to avoid confounding with patients treated for adenocarcinoma of the esophagus or gastroesophageal junction.

Definition of Specific Measures

Patient characteristics were identified from SEER registry data. Comorbidity data were determined by the Deyo method to calculate Charlson comorbidity score using hospital and physician claims data in the 12 months prior to diagnosis [14–16]. Hospital characteristics were determined at the date of the surgery claim submission using the hospital file.

Inpatient, outpatient, and physician claims files were used to identify receipt of chemotherapy and radiation therapy. Prior studies have demonstrated that the sensitivity of using Medicare claims to identify chemotherapy use is high (88%) and agreement between SEER data and Medicare claims for radiation therapy is also very good (88%) [17,18].

In the current study, receipt of peri-operative chemotherapy was defined as any chemotherapy, without radiation, received between the date of diagnosis and date of surgery with or without additional chemotherapy 90 days after surgery. Receipt of post-operative CRT was defined as any chemotherapy with radiation therapy, received within 90 days after surgery. The analytic cohort was then restricted to patients treated in 2002 or later to correspond to publication of INT-0116. Patients were assigned to one of two groups: evidence-based treatment, defined as either peri-operative chemotherapy or post-operative CRT, or non-evidence-based treatment, defined as resection and observation or any other adjuvant regimen.

Receipt of chemotherapy was identified within the Outpatient and Carrier Medicare files using specific Healthcare Common Procedure Coding System Codes (HCPCS), ICD-9, and revenue center codes. Receipt of radiation therapy was determined in PEDSF and in the MEDPAR and Outpatient Medicare files using ICD-9, CPT, and revenue center codes. Consultation with a medical oncologist was determined by searching for Health Care Financing Administration provider specialty codes from the date of diagnosis to 90 days after surgery (Appendix 1).

Post-operative morbidity was determined by identification of ICD-9 codes for relevant post-operative complications, including re-exploration, hemorrhage, anemia, dehiscence, peritonitis, anastomotic disruption, intestinal fistula, infection, ileus, post-gastric surgery syndrome, delayed gastric emptying, and gastric outlet obstruction, indicated within the same inpatient stay as the initial resection.

Statistical Analysis

Comparisons between treatment groups on patient demographic and clinical characteristics were performed using χ^2 tests (categorical variables) and Wilcoxon-rank sum tests (continuous variables). Using a multivariable logistic regression model to control for covariates selected *a priori*, odds ratios (OR) and 95% confidence intervals (CI) were calculated for associations with receipt of evidence-based or non-evidence based therapy. Goodness of fit of the logistic regression model was assessed with the Hosmer and Lemeshow test and also with area under the Receiver Operating Characteristics Curve [19]. All P-values were 2-tailed and were considered statistically significant if $P < 0.05$. All analyses were performed using SAS statistical software, version 9.2 (SAS Inc., Cary, NC).

Results

Treatment Trends over Time

The final cohort was comprised of 4841 patients. The majority of all patients underwent surgery alone (60.9%; N=2946). Only 19.1% (N=925) received post-operative CRT and 1.9% (N=90) received peri-operative chemotherapy.

Three time periods (1991–2001, 2002–2005, and 2006–2009) were defined to correspond to post-publication dates of the INT-0116 (2001) and MAGIC trials (2006). The proportion of patients treated with post-operative CRT increased significantly after trial publication as did the proportion of patients treated with peri-operative chemotherapy ($P<0.001$) (Table 1).

Use of Evidence-Based Multimodality Treatment

The cohort was then limited to patients treated in 2002–2009 ($N=2453$) to correspond with publication of INT-0116. Less than 3% of patients with Stage IB disease received peri-operative chemotherapy, and only 12.5% ($N=87$) received post-operative CRT. A greater proportion of patients with Stage II disease were treated with post-operative CRT (28.7%; $N=217$), although the proportion of patients treated with peri-operative chemotherapy remained low (3.0%; $N=23$). A similar distribution was seen among patients with Stage III and IV (M0) disease (Table 2).

Comparison of patients who received evidence-based care to patients who received non-evidence-based care revealed some notable differences (Table 3). Patients treated with evidence-based therapy were younger, male, had a higher stage disease, and a lower Charlson comorbidity score ($P<0.01$). A significantly larger proportion of patients treated with an evidence-based regimen also had a billing claim for a medical oncology consultation (89.1% vs 68.1%) ($P<0.001$). However, even among patients who consulted with medical oncology, only 33.7% ($N=612$) received evidence-based care.

We found that patients who underwent consultation with medical oncology were more likely to be younger ($P<0.001$), male ($P=0.001$), and Caucasian ($P=0.04$), and to have later stage disease ($P<0.001$). We did not identify any differences by Charlson score, urban or rural patient residence, or income level. A significant association was identified by SEER region, with patients in the West region less likely to undergo medical oncology consultation compared to other SEER regions ($P=0.004$).

The median number of LN resected was higher among patients treated with evidence-based care (13 vs. 11; $P<0.001$). However, there was no difference in post-operative morbidity rates. Additionally, there were no significant differences when comparing hospital factors between the two groups, including NCI designation status or American Medical Association (AMA) residency program affiliation (Table 4).

Patients treated at an NCI center were more often younger ($P=0.007$) and were more often treated in the Northeast and North Central SEER regions ($P<0.001$). We found no association between Charlson comorbidity score and treatment at an NCI center ($P=0.198$).

Factors Associated with Evidence-based Multimodality Treatment

A multivariable logistic regression model was used to identify factors associated with receipt of evidence-based treatment while controlling for confounding variables (Table 5). No evidence of lack of fit was found based on Hosmer and Lemeshow test (Chi-squared value=10.3, degrees of freedom=8, and P -value=0.25). Area under the ROC curve was 0.75 (95% CI 0.73–0.77), also indicating this model's goodness of fit. The effect of age, stage, and Charlson comorbidity score remained significant, with elderly patients (> 75 years of

age) less likely to receive evidence-based therapy than younger patients (age 66; OR 0.38, 95% CI 0.33–0.45) and patients with higher stage disease (Stage II) more likely to receive evidence-based therapy ($P<0.01$). Additionally, patients who had a consultation with a medical oncologist were significantly more likely to receive evidence-based treatment (OR 3.10, 95% CI 2.35–4.09). However, there was no significant association with other covariates, such as treatment at an NCI center.

Discussion

Despite the publication of two large RCTs demonstrating a significant survival benefit of surgery with either peri-operative chemotherapy or post-operative CRT, utilization of these two treatment regimens remains remarkably low in the U.S. Notably, in this study, the proportion of patients with Stage IB disease treated with surgery alone remains high, despite evidence supporting the use of adjuvant therapy in this population. Our study also shows that elderly patients and patients with a higher Charlson comorbidity index are less likely to receive evidence-based treatment than younger or healthier patients. Contrary to our hypothesis, we found no association between NCI designation status and administration of multimodality therapy. Finally, we demonstrate that patients who consulted with a medical oncologist were more than three times as likely to receive treatment based on RCT evidence than patients who never saw an oncologist.

Prior studies have demonstrated low rates of administration of post-operative CRT among gastric cancer patients, even after the results of INT-0116 were published in 2001 [7,8,20]. This study confirms these findings, with only 25.1% of eligible patients receiving post-operative CRT from 2002–2009. Little is known, however, about the use of neoadjuvant or peri-operative chemotherapy rates after publication of the MAGIC trial. One recent study demonstrated an increase in neoadjuvant therapy from 5.9% in 1998 to 20.0% in 2007; however, this study included neoadjuvant CRT, most of which was delivered to patients with tumors of the cardia (80%) [21]. Our findings demonstrate a much lower rate of neoadjuvant therapy use (2.9% from 2002–2009) when excluding patients who underwent esophagectomy and using a strict definition of peri-operative chemotherapy alone (without radiation), which is more consistent with the MAGIC regimen.

There are a number of hypotheses that might explain the under-treatment of gastric cancer patients despite high quality evidence supporting its use. The adoption of new standards of care may depend on a number of factors, including the timeliness of information dissemination, the economic impact of treatment, and the availability of resources and expertise. Because the incidence of gastric cancer is lower than other cancers, it is possible that few institutions are true “expert” institutions, leading to a lack of standardized processes of care. The availability of multidisciplinary expertise may also differ significantly across institutions, resulting in greater variation in care. Also, because the patients enrolled in INT-0116 and MAGIC trials were highly selected for trial eligibility, they may differ from the general gastric cancer patient population who may have a worse performance status, and be less ideal candidates for adjuvant therapy. Hoffman *et al* did not find a survival benefit of chemoradiation among the Medicare population, suggesting that not all patients who qualify for adjuvant therapy will benefit, although this type of retrospective survival analysis should

be interpreted cautiously. In addition, it is possible that patients treated in the community may have higher post-operative complication rates than patients treated in an RCT, which could prevent them from receiving post-operative therapy at the same frequency.

Our findings also suggest that patients with early stage, Stage IB disease, are more likely to be undertreated in the U.S. than those with more advanced disease. Although patients with Stage IB were included in the INT-0116 trial, the number of patients was small (N=36), and the trial was underpowered to detect stage-specific survival differences [22]. Additionally, an observational study using SEER-Medicare data found no survival advantage of CRT among Stage IB patients [23]. Given that survival among patients with Stage IB disease is significantly better than later stage gastric cancers, providers may be less convinced of the benefits of multimodality therapy in this population [24].

Prior studies have indicated that the profile of the treating hospital may have a significant influence on the surgical treatment and outcomes of patients with gastric cancer. Patients treated at an NCI center are more likely to undergo an adequate LN dissection (> 15 lymph nodes) [10,11]. Similarly, two studies of Commission on Cancer (CoC) hospitals identified an association between teaching hospital status and adequacy of LN dissection [25,26]. Birkmeyer *et al.* also demonstrated improved operative mortality and a trend towards improved long-term survival among patients with gastric cancer treated at NCI centers compared with other hospitals [12].

However, there is little evidence to suggest that expert centers, such as NCI or CoC hospitals, or teaching hospitals are associated with higher rates of administration of multimodality therapy. According to two analyses of NCDB data, chemotherapy and radiation therapy are utilized with equal frequency at CoC community and teaching hospitals for the treatment of gastric cancer [25,26]. Our data support a similar conclusion, in that patients treated at an NCI center appear no more likely to be treated with evidence-based multimodality therapy than patients treated at other hospitals.

There are limitations of using SEER-Medicare data in our study. First, use of an administrative dataset introduces the bias of potential coding inaccuracies, missing data, and variation in billing practices. Additionally, SEER-Medicare does not include margin status or performance status. Because our cohort was confined to only those patients with a billing code for gastrectomy, it is possible that we may have underestimated rates of pre-operative chemotherapy. Some patients may have experienced disease progression on neoadjuvant treatment, making them ineligible for resection, and therefore excluded from our cohort. Using Medicare data, we cannot assess for trends among younger patients. However, given that 62% of patients diagnosed with gastric cancer each year are >65, the dataset is representative overall of this disease population [13]. However, we recognize that the patterns of care for younger patients may differ, and our results may not be generalizable to the younger population. Finally, Medicare data do not include information about care provided by non-Medicare providers (such as Veterans Affairs), or for which Medicare was not employed as the primary insurance.

Conclusions

In conclusion, despite high-quality RCT evidence supporting the use of post-operative CRT or peri-operative chemotherapy for resected gastric cancer, utilization rates remain remarkably low. This may, at least partially, explain the poor survival rates for gastric cancer in the U.S. Utilization of peri-operative chemotherapy remains especially low, even after results of the MAGIC trial were reported in 2006. Because gastric cancer trials are historically slow to accrue patients, a survival analysis comparing the INT-0116 and MAGIC regimens using administrative data would be highly informative, although difficult to perform with so few patients receiving peri-operative chemotherapy to date.

Based on this study, there is no difference in the administration of evidence-based treatment between NCI designated cancer centers and other hospitals. Future studies are needed to explore the reasons for omission of multimodality treatment in depth. We did find that patients who underwent a consultation with a medical oncologist were more likely to receive appropriate therapy than patients who did not see an oncologist. An investigation into referral patterns and the timing of consultation may shed some light on this critical step in the care pathway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Trends in use of multimodality therapy over time (N=4841).

	1991–2001	2002–2005	2006–2009	P-value
Any preoperative chemotherapy	0.8% (18)	1.5% (20)	4.7% (52)	<0.001
Post-operative chemoradiation	13.0% (310)	24.8% (333)	25.4% (282)	<0.001
Surgery alone	68.7% (1641)	55.5% (746)	50.4% (559)	<0.001
Other	17.6% (419)	18.2% (245)	19.5% (216)	0.386
Total	100% (2388)	100% (1344)	100% (1109)	----

Table 2

Proportion of patients receiving treatment by stage 2002–2009 (N=2453).

AJCC Stage	Perioperative chemotherapy	Post-operative chemotherapy	Post-operative radiation	Post-operative chemoradiation	Surgery alone
IB	2.9% (20)	5.9% (41)	3.3% (23)	12.5% (87)	72.4% (503)
II	3.0% (23)	11.3% (85)	3.3% (25)	28.7% (217)	50.6% (382)
III	3.2% (24)	13.1% (98)	5.2% (39)	32.2% (241)	42.5% (318)
IV (M0)	2.0% *	22.0% (56)	5.1% (13)	27.5% (70)	40.0% (102)

* Numbers not shown to protect confidentiality.

Note: An additional 81 patients were treated according to a regimen other than the categories listed above.

Table 3

Patient demographics and clinical characteristics, 2002–2009 (N=2453).

	Evidence-based care: (687)	Non-evidence based care: (1766)	P-value
Median age (quartiles)	72 (69, 77)	78 (72, 83)	<0.001
Gender			
Male	62.3% (428)	55.0% (971)	0.001
Race			
White	61.6% (423)	65.6% (1158)	0.292
Black	13.5% (93)	11.6% (204)	
Asian	13.1% (90)	12.2% (216)	
Other/Hispanic	11.8% (81)	10.6% (188)	
Year of diagnosis			
2002	12.8% (88)	14.6% (257)	0.135
2003	13.5% (93)	12.9% (228)	
2004	11.8% (81)	15.9% (280)	
2005	13.2% (91)	12.8% (226)	
2006	13.5% (93)	12.5% (220)	
2007	11.1% (76)	11.4% (201)	
2008	12.7% (87)	10.8% (190)	
2009	11.4% (78)	9.3% (164)	
Tumor site			
Cardia/Fundus	16.2% (111)	17.5% (309)	0.170
Body/Antrum	29.1% (200)	25.1% (443)	
Other	28.8% (198)	28.7% (506)	
Missing	25.9% (178)	28.8% (508)	
Stage			
Stage IB	15.6% (107)	33.3% (588)	<0.001
Stage II	34.9% (240)	29.2% (515)	
Stage III	38.6% (265)	27.3% (483)	
Stage IV (M0)	10.9% (75)	10.2% (180)	
Charlson co-morbidity index			
0	49.3% (339)	39.5% (698)	<0.001
1	27.8% (191)	35.5% (627)	
2+	22.9% (157)	25.0% (441)	
Patient residence			
Rural	7.4% (51)	7.7% (136)	0.816
Urban	92.6% (636)	92.3% (1630)	

	Evidence-based care: (687)	Non-evidence based care: (1766)	P-value
Income level			
Quartile 1 (\$35,149)	23.7% (163)	26.2% (462)	0.486
Quartile 2 (\$35,150–\$46,348)	25.2% (173)	23.8% (421)	
Quartile 3 (\$46,349–\$60,306)	21.4% (147)	22.7% (401)	
Quartile 4 (\$60,307)	25.8% (177)	23.1% (408)	
Missing	3.9% (27)	4.2% (74)	
SEER Region			
West	47.5% (326)	44.7% (789)	0.333
Northeast	23.0% (158)	24.1% (425)	
South	20.2% (139)	19.7% (348)	
North Central	9.3% (64)	11.6% (204)	
Med oncology consultation	89.1% (612)	68.1% (1203)	<0.001

Surveillance Epidemiology and End Results (SEER).

Table 4

Surgical and hospital characteristics and post-operative outcomes 2002–2009 (N=2453).

	Evidence-based care (N=687)	Non-evidence based care (N=1766)	P-value
Type gastrectomy			
Total	29.4% (202)	30.6% (541)	0.551
Distal or partial	70.6% (485)	69.4% (1225)	
Median number of LN resected (quartiles)	13 (7, 20)	11 (6, 18)	<0.001
LN resected*			
0–10	38.7% (266)	47.0% (830)	<0.001
11–20	35.4% (243)	31.9% (564)	
21	24.0% (165)	18.3% (323)	
Treatment at teaching hospital*	64.1% (440)	62.9% (1111)	0.715
Treatment at NCI Cancer Center*	9.6% (66)	8.2% (145)	0.448
Treating hospital affiliated with a medical school*	56.3% (387)	56.6% (1000)	0.815
Treating hospital affiliated with an AMA approved residency program*	36.5% (251)	38.0% (671)	0.653
Post-operative morbidity			
0	76.4% (525)	75.2% (1328)	0.779
1	19.1% (131)	19.8% (349)	
2	4.5% (31)	5.0% (89)	

Lymph node (LN), National Cancer Institute (NCI), American Medical Association (AMA).

* Missing values not reported when fewer than 3.0% of patients to protect confidentiality.

Table 5

Factors associated with receipt of evidence-based multimodality therapy 2002–2009 (N=2390).*

	Proportion Receiving Evidence- Based Treatment (N=674)	Proportion Receiving Other Regimen (N=1716)	Adjusted OR for Evidence-Based Treatment (95% CI)	P-value
Age				
66	--	--	Reference	<0.001
70	--	--	0.65, 0.61–0.70	
75	--	--	0.38, 0.33–0.45	
Sex				
Male	62.0% (418)	54.7% (939)	Reference	0.085
Female	38.0% (256)	45.3% (777)	0.84, 0.69–1.03	
Race				
White	61.4% (414)	65.6% (1126)	Reference	0.562
Black	13.5% (91)	11.5% (197)	1.10, 0.81–1.49	
Asian	13.2% (89)	12.2% (210)	1.16, 0.84–1.61	
Other/Hispanic	11.9% (80)	10.7% (183)	0.97, 0.70–1.35	
Year of diagnosis				
2002	--	--	Reference	0.068
2003	--	--	1.04, 1.00–1.09	
2004	--	--	1.09, 0.99–1.18	
2005	--	--	1.13, 0.99–1.29	
2006	--	--	1.18, 0.99–1.40	
2007	--	--	1.23, 0.99–1.53	
2008	--	--	1.28, 0.98–1.66	
2009	--	--	1.33, 0.98–1.81	
SEER region				
West	47.5% (320)	44.8% (769)	Reference	0.817
Northeast	22.9% (154)	23.7% (407)	0.97, 0.74–1.28	
South	20.3% (137)	19.9% (341)	0.80, 0.60–1.07	
North Central	9.4% (63)	11.6% (199)	0.79, 0.55–1.15	
Stage				
Stage IB	15.6% (105)	33.2% (569)	Reference	<0.001
Stage II	35.0% (236)	29.3% (503)	2.55, 1.93–3.37	
Stage III	38.3% (258)	27.3% (469)	2.58, 1.95–3.40	
Stage IV (M0)	11.1% (75)	10.2% (175)	1.80, 1.24–2.62	
Number of LN resected				
10	--	--	Reference	0.249

	Proportion Receiving Evidence- Based Treatment (N=674)	Proportion Receiving Other Regimen (N=1716)	Adjusted OR for Evidence-Based Treatment (95% CI)	P-value
20	--	--	1.05, 0.96–1.15	
30	--	--	1.11, 0.93–1.32	
Charlson comorbidity index				
0	49.6% (334)	39.3% (674)	Reference	
1	23.4% (188)	35.8% (614)	0.54, 0.41–0.71	<0.001
2+	22.6% (152)	24.9% (428)	0.75, 0.56–1.01	0.032
Treatment at NCI center				
No	90.4% (609)	91.8% (1575)	Reference	
Yes	9.6% (65)	8.2% (141)	1.05, 0.74–1.49	0.770
Treatment at hospital affiliated with residency				
No	43.6% (294)	43.0% (738)	Reference	0.491
Yes	56.4% (380)	57.0% (978)	0.93, 0.75–1.15	
Consultation with medical oncologist				
No	11.0% (74)	31.9% (548)	Reference	
Yes	89.0% (600)	68.1% (1168)	3.10, 2.35–4.09	<0.001

Odds ratio (OR), Confidence interval (CI), Surveillance Epidemiology and End Results (SEER), Lymph node (LN), National Cancer Institute (NCI).

* Patients with any missing values excluded from multivariable model (N=63).