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Surgical Management of Advanced Non-Small Cell Lung Cancer is Decreasing but is Associated with Improved Survival

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Abstract

Background—For patients with advanced stage Non—Small Cell Lung Cancer (NSCLC), chemotherapy and chemoradiation are the principal treatment modalities, and the role of surgical resection remains unclear. Our objective was to evaluate current trends and oncologic outcomes in advanced stage NSCLC. We hypothesized that surgery is associated with increased survival and may be an underutilized treatment modality.

Methods—The California Cancer Registry was queried from 2004–2012 for cases of stage IIIA, IIIB, and IV NSCLC, and we identified 34,016 cases. Patients were categorized by treatment group, and linear regression was used to calculate trends in treatment and predictors of treatment group. Kaplan-Meier and Cox regression modeling were used to determine the influence of treatment group on overall (OS).

Results—Twenty- seven percent (9223/34,016) of patients received no treatment. For the entire cohort, treatment with chemotherapy alone increased ($p < 0.001$), but treatment with radiation alone, surgery alone or in any combination decreased ($p=0.011$, <0.001, 0.021, 0.007, and 0.094) Treatment group, age, sex, race, socioeconomic status, stage, histology, and tumor size were all significant predictors of OS. OS was significantly longer in patients who had surgery as part of their treatment regimen ($p<0.001$).

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Conclusions—For patients with advanced stage NSCLC, the use of multimodality regimens that include surgery are decreasing despite longer OS. Future studies are needed to identify the demographics and clinical characteristics of patients with advanced stage NSCLC who may benefit from surgery.

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality in developed countries for both sexes worldwide, accounting for more than 1.4 million deaths per year[1]. Unfortunately, the vast majority (79%) of patients are diagnosed with stage IIIA, IIIB or IV disease, which dramatically reduces the chance for cure or meaningful survival[2]. Overall five-year survival for all patients with NSCLC is approximately 17.4%, but varies by stage [2]. Meaningful long-term survival is typically limited to patients with localized disease who are candidates for surgical resection. Surgery only with curative intent, for select stage IIIa and IV patients, in combination with other treatment modalities, but is not currently recommended for stage IIIb patients.

Under the current guidelines, there are circumstances in which patients with stage IIIA or IV NSCLC are eligible to undergo surgical resection, in the context of a multimodality approach [3]. Retrospective studies have observed improved survival among advanced stage NSCLC patients who have received surgical therapy [4–12]. An analysis of National Cancer Database (NCDB) data demonstrated increased survival for stage IIIA patients who have surgery included in their treatment regimen. However, this analysis also showed that few of these patients received surgical resection (14%) [13]. Similarly, for Stage IIIB (defined as T4N2 or any N3) patients, the incorporation of surgery into multidisciplinary treatment is associated with increased survival. The increased survival observed with surgery persisted after adjusting for confounding variables including receipt of chemotherapy and radiotherapy in a propensity-matched analysis of the NCDB [10]. Among patients with Stage IV disease who harbor limited disease burden or oligometastatic disease, surgical management has also been associated with increased survival [14,15]. The increased survival seen in these circumstances has been attributed to selection bias leading to patients with better performance status and/or more limited metastatic burden undergoing surgery. It has been difficult to objectively measure the extent and mechanism of selection bias using using large cancer registries because they lack granular patient data to fully characterize differences in treatment allocation to explain this selection bias. Despite the trend for increased survival in patients undergoing surgery as part of a multimodality approach, the use of surgery in this population is generally low. Therefore, we sought to characterize the trends in treatment of advanced stage NSCLC and characterize the oncologic outcomes. We hypothesized that surgery is associated with increased survival and may be an underutilized treatment modality for appropriately selected patients.

Patients and Methods

This study was exempt by the University of California, Davis IRB. Patients were identified through the California Cancer Registry (CCR), which includes data for the entire population of California. The CCR is a participant in the National Cancer Institute Surveillance Epidemiology and End Results (SEER) program, the only comprehensive source of

population-based information in the US which includes stage of cancer at the time of diagnosis and rigorous survival data.

Data in the CCR are abstracted from medical records and include patient demographics, tumor characteristics, and type of surgical resection. Race/ethnicity in the CCR is based on information collected from medical records supplemented with linkage to algorithms to appropriately identify Hispanics and Asian/Pacific Islanders. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, and non-Hispanic Asian/Pacific Islander. Patient address at diagnosis is assigned to a census tract, and neighborhood socioeconomic status (SES) was based on U.S. Census characteristics combined into the summary Yost index, categorized into quintiles [16].

Only patients for whom NSCLC was the first or only cancer diagnosis and who had invasive adenocarcinoma or squamous cell carcinoma were included. Patients diagnosed at autopsy were excluded from analysis. Stage at diagnosis was defined based on the SEER modification of the American Joint Committee on Cancer staging system. Patients diagnosed as stage III or IV from 2004–2012 were included in this analysis. In the CCR, stage refers to clinical stage for patients who have not had surgery and pathologic stage for patients who have had surgery, if complete staging information is available. Patients were followed through December 31, 2012.

Types of treatment included No Treatment (NTX); Chemotherapy only (Chemo); Radiation only (Rad); Chemoradiation (CR); Surgery only (SURG); Chemotherapy and Surgery (CS); Surgery and Radiation (SurgRad); Chemotherapy, Radiation, and Surgery (CRS); and Unknown (UNK). Types of surgery included sublobar resection (wedge and segmentectomy), lobectomy, and bilobectomy/pneumonectomy. Chi-square tests were used to determine whether baseline characteristics in demographic characteristics and treatment were significantly different between the treatment groups. Linear regression analysis was used to determine the trend in treatment over the study period; using the proportion of patients who received treatment at a certain year as a continuous variable as the outcome. Overall survival (OS) and cancer-specific survival (CSS) functions were estimated using Kaplan-Meier method within treatment groups. Log-rank tests were conducted to examine whether the unadjusted differences in survival between the groups were statistically significant. Multivariable Cox proportional hazard regression analysis was performed for OS and CSS, adjusting for patient’s age, sex, race, SES, stage, tumor size, and histology. Nominal logistic regression analysis was conducted to evaluate the relationship of predictor variables to treatment groups as the outcome variable, adjusting for significant covariates. Parallel analyses were performed for surgery subgroups. We considered p-values less than 0.05 as statistically significant. All statistical analyses were conducted using SAS for Windows, version 9.3 (SAS Institute Cary, NC).

Results

As shown in Table 1, we identified 34,016 patients diagnosed from 2004–2012 with Stage III or IV NSCLC. The majority of the patients were non-Hispanic white (65%), more than half were male, and patients were evenly distributed by SES category.

Figure 1 shows 27% of patients received no treatment for NSCLC, and the percentage of patients receiving no treatment increased commensurate with stage (Table 2, $p<0.0001$). Chemoradiation was the next most common treatment (25.7%). Surgery alone or in combination with any other treatment was performed in 11% of the cohort in aggregate. The treatment groups were heterogeneous for age, sex, race, SES, and stage.

Frequency of Treatment Group Trend Analysis

For the entire cohort, there was a 0.6% increase in treatment with chemotherapy over time ($p<0.001$), but treatment with radiation alone, surgery alone, or surgery in combination with any other treatment modality decreased over the study period (Table 3). For patients with Stage IIIA disease, there was a significant increase in patients receiving no treatment and a significant decrease in patients receiving chemotherapy plus surgery (Figure 2A). Among patients with Stage IIIB disease, there was a significant increase in treatment with chemoradiation (Figure 2B). Treatment with surgery alone or in any combination significantly decreased as did the incidence of no treatment. For patients with Stage IV disease, there was no change in the incidence of no treatment whereas treatment with chemotherapy increased, and treatment with radiation alone or surgery alone or in any combination significantly decreased (Figure 2C).

For patients who had surgery in any combination, the frequency of lobectomy increased over the study ($p=0.014$) the frequency of bilobectomy/pneumonectomy decreased ($p=0.039$) (data not shown).

Survival Analysis

Survival, both OS and CSS, was significantly longer in all of the groups that included surgery ($p<0.0001$) (Figure 3) (data not shown for CSS). For the entire cohort, median OS was 40.7 months for patients treated with CS, 33.3 months for patients treated with CRS, 28.8 months for patients treated with SURG, and 18.6 months for SurgRad. In the patients who did not have surgery, median OS was 11.9 months for CR, 10.5 months for Chemo, 3.7 months for RAD and 2.1 months for NTx. Stage specific median OS is shown in Table 4. We observed the same pattern of longer OS in patients receiving surgery as part of their treatment across stages. On multivariate analysis, treatment group, age, sex, race, SES, stage, histology and tumor size were all significant predictors of OS and CSS (Table 5) (data not shown for CSS).

Predictors of treatment group

Multivariable nominal regression was performed with treatment group as the outcome variable to examine factors predictive of receipt of individual treatments (Table 6). With increasing age, patients were more likely to receive NTx versus CR, Chemo, Rad or any surgical treatment. When compared to the highest SES, patients in all other SES categories were significantly more likely to undergo NTx than CR, Chemo, Rad or any surgical treatment. Patients with Stage IIIB or IV disease were significantly more likely to undergo NTx than CR, Rad or any surgical treatment, compared to stage IIIa.

Comment

We analyzed the patterns of treatment for advanced stage NSCLC and identified that 27% of advanced stage NSCLC in CA undergo NTx for their disease. Many factors impact the decision to undergo NTx and it is possible that because of under-reporting to the registry the size of this group may have been overestimated. Yet, disparities in receipt of therapeutic treatment have been observed in early stage NSCLC, so it is likely that disparities in access to care contributed to the high rates of NTx. The negative perceptions of lung cancer outcomes by patients and physicians may also influence the decision for NTx in our cohort.

Poor survival rates and stigma are associated with NSCLC and likely perpetuate themselves and impact treatment decisions for NTx. In a survey of primary care physicians, Wassenaar et al found significant differences in referral patterns and a lack of knowledge regarding treatment options and outcomes among in the primary care community regarding the benefits of treatment of NSCLC[17]. In a Swedish study of treatment trends of all stages of NSCLC, 33.4% of patients underwent no treatment and there were significant differences in treatment trends based on region of treatment[18]. These authors observed that increasing age was a significant predictor of not receiving treatment. Additionally, Hispanic and Black race were associated with increasing rates of no treatment, as was lower SES; suggesting that disparities of care may influence the number of patients receiving no treatment for NSCLC.

Racial disparities in the care of NSCLC patients are well established and have proven difficult to ameliorate. In a study of early-stage NSCLC patients in 1999, Bach et al demonstrated that lower survival rates in black patients could be attributed to lower rates of surgery in these patients[19]. Given that SES and race/ethnicity predicted no treatment in our analysis, our data suggest these racial disparities also affect outcomes in advanced stage NSCLC.

Overall MST was significantly longer for patients in any of the treatment groups that involved surgery. However, the incidence of surgery was low at 10.8% and decreased over time. In the NCDB, rates of surgery for stage IIIA disease range from 12–17% and from 12–18.5% for stage IIIB disease [10,13]. These studies demonstrate increased survival in the surgical cohorts. It is highly likely that longer survival in the surgical cohorts represents selection bias for healthier patients with fewer comorbid conditions, but this is difficult to assess. A propensity-matched analysis of the stage IIIB NCDB patients, demonstrated longer survival in patients treated with CRS compared to CR (28.9 months vs 17.2 months, $p<0.001$) suggesting that the surgical survival advantage may not be solely due to selection bias and could represent a treatment effect [10].

It is interesting to speculate why the utilization of surgery is decreasing. It is possible that improved systemic therapies are changing initial treatment approaches, but some have suggested that favorable response to systemic therapy may make more patients eligible for surgery. n analysis of an Englishcancer registry demonstrated a similar decrease in the use of surgery for all stages of NSCLC from 1995–2006 [20]. These authors attributed the decrease in use of surgery to improvements in radiological staging, but this explanation would likely

undermine our fundamental observation of an association of surgery with improved OS. It is possible that the decreased use of surgery over time in our study reflects changing referral patterns and a lackof surgical involvement in multidisciplinary treatment planning for these patients., There are limitations to this study. As with any registry analysis, we are unable to explain treatment decisions or the intent of the treatments administered. Chemotherapy data are known to be underreported to the CCR. It is possible that patients in the SurgRad group may have received chemotherapy, thereby explaining the high survival in that cohort. Additionally, only 20% of patients had lymph node sampling, which may reflect a significant understaging of NSCLC patients in the CCR.

The association of surgery with improved survival in advanced stage NSCLC is recognized by most thoracic surgeons, but it is unclear whether or not this association has been disseminated to other providers and disciplines involved in the care of NSCLC patients. Association clearly does not prove a causal relationship. It is important to assess all patients with NSCLC in a multidisciplinary context for possible surgical candidacy. There may be an opportunity to extend surgical intervention in advanced stage NSCLC to a larger proportion of appropriately selected patients, particularly those who are older, from lower SES groups, and from under-represented minority groups.

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Abbreviations

NSCLC	Non-small cell lung cancer
NCDB	National Cancer Database
CCR	California Cancer Registry
SEER	Surveillance Epidemiology and End Results
SES	Socioeconomic Status
NTX	No Treatment
Chemo	Chemotherapy only
Rad	Radiation only
CR	Chemoradiation
Surg	Surgery only
CS	Chemotherapy and Surgery
SurgRad	Surgery and Radiation

CRS	Chemotherapy, Radiation, and Surgery
UNK	Unknown Treatment
OS	Overall survival
CSS	Cancer specific survival

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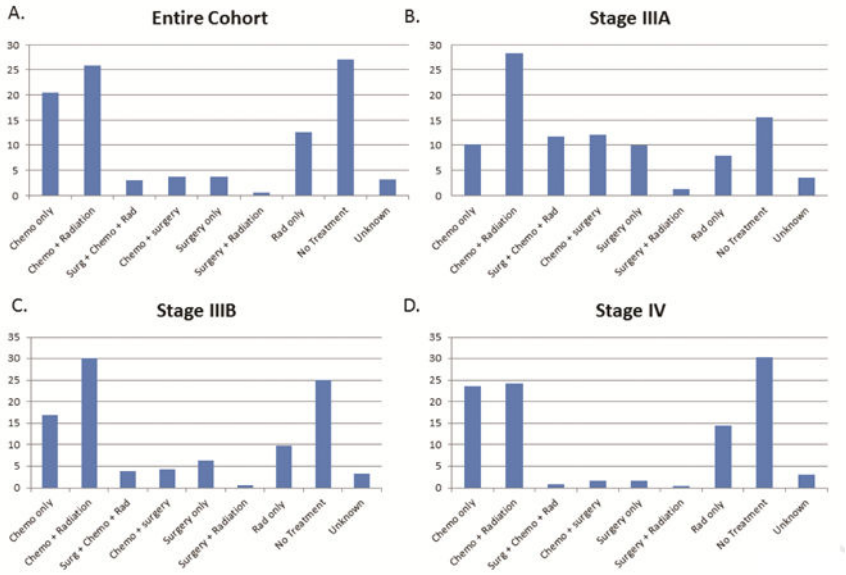

Figure 1.

Distribution of treatment groups overall and by stage. A. Overall Cohort. B. Stage IIIA C. Stage IIIB D. Stage IV

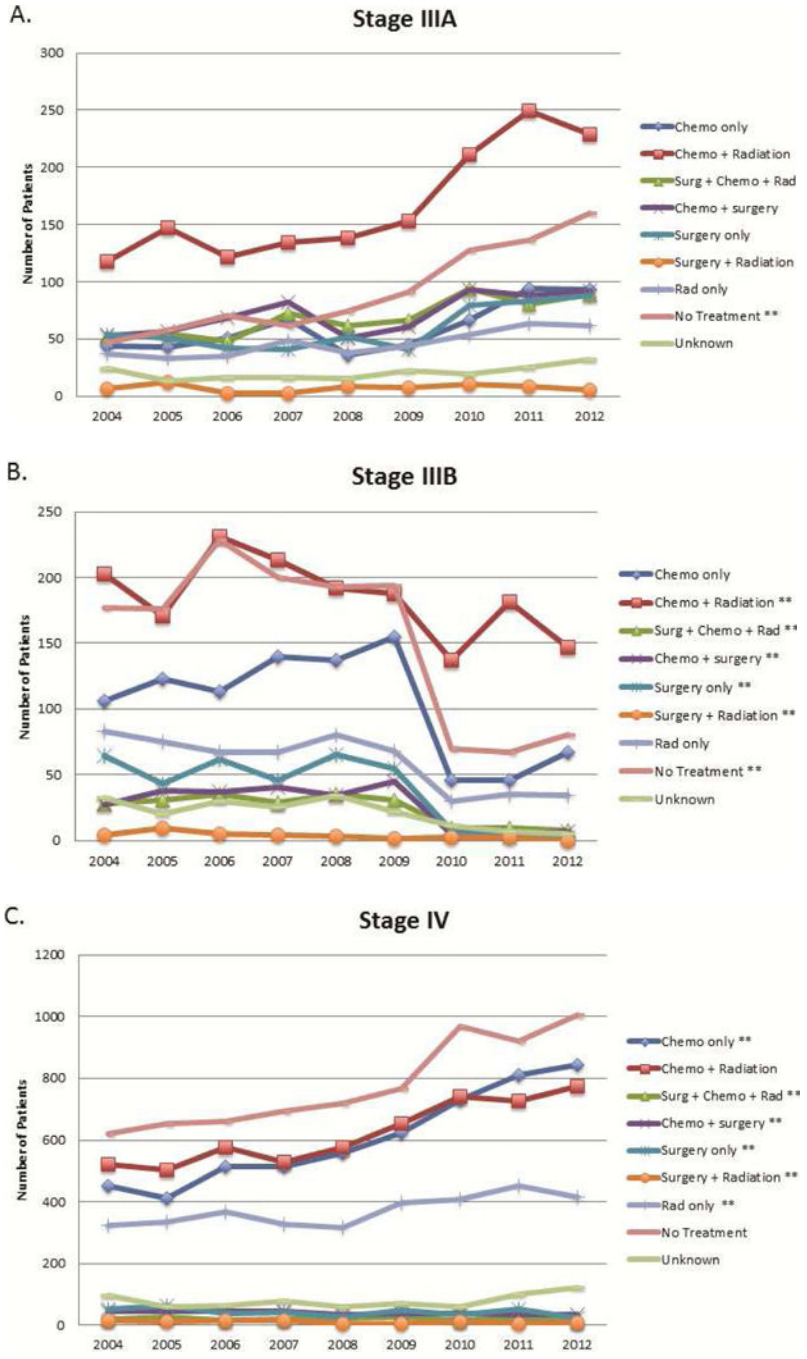

Figure 2.

Distribution of treatment groups by Year. A. Stage IIIA B. Stage IIIB C. Stage IV ** denotes trend is significant ($p<0.05$)

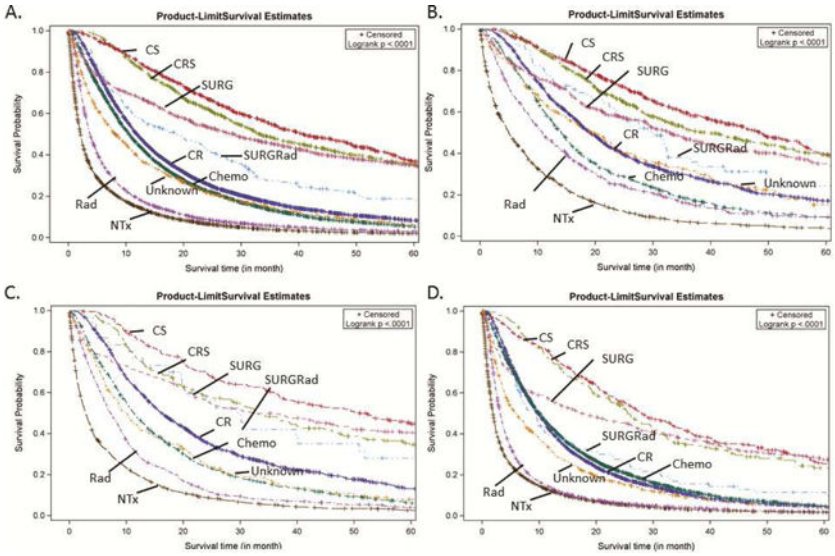

Figure 3.

Kaplan-Meier plots for Overall Survival. A. Entire cohort. B. Stage IIIA. C. Stage IIIB. D. Stage IV.

Table 1

Characteristics of Stage III and IV patients diagnosed with NSCLC from 2004–2012 in California

Predictors	N (%)
Age	
Less than 65	12877 (37.7)
65–74	10930 (32.13)
75+	10209 (30.01)
Gender	
Male	18438 (54.2)
Race	
White	22114 (65.0)
Black	2974 (8.7)
Hispanic	4126 (12.1)
Asian/Pacific Islander	4537 (13.3)
Others/Unknown	265 (0.78)
Socioeconomic Status	
Lowest	5748 (17.4)
Lower-middle	7006 (21.2)
Middle	7332 (22.2)
Higher-middle	7130 (21.6)
Highest	5830 (17.6)
Clinical Stage	
IIIA	5319 (15.6)
IIIB	5536 (16.3)
IV	23161 (68.1)
Tumor Size	
<20 mm	2827 (8.3)
20–30 mm	4056 (11.9)
30–50 mm	8192 (24.1)
50–70 mm	5688 (16.7)
>70 mm	13253 (38.9)
Lymph nodes Examined	
No	27142 (79.8)
Yes	6652 (19.6)

Table 2

Distribution of patients diagnosed with NSCLC in California, 2004–2012. N=row percent

Patient Characteristics	No Treatment (N=9223)	Chemotherapy only (N=6930)	Radiation only (N=4299)	Chemotherapy And Radiation (N=8768)	Surgery only (N=1261)	Chemotherapy And Surgery (N=1243)	Surgery And Radiation (N=189)	Surgery and Chemotherapy and Radiation (N=1022)	Unknown (N=1081)	p-value
Age										
<65	18.8	21.1	10.9	33.9	2.6	4.3	0.5	4.4	3.5	<0.0001
65–74	25.5	21.4	12.2	25.6	4.2	4.2	0.6	3.1	3.2	<0.0001
75+	39.3	18.4	15.3	15.8	4.6	2.2	0.6	1.1	2.8	<0.0001
Gender										
Male	27.5	19.7	13	26.6	3.4	3.2	0.5	2.7	3.3	<0.0001
Female	26.7	21.1	12.2	24.8	4	4.2	0.6	3.3	3.1	<0.0001
Race										
White	26.6	19.4	13.2	26	4	3.8	0.6	3.1	3.2	<0.0001
Black	30.2	20.1	13.2	25.3	2.8	2.9	0.3	2.3	2.9	<0.0001
Hispanic	30.3	21.1	11.8	23.8	3.3	3.3	0.5	2.5	3.5	<0.0001
Asian/Pacific Islander	24.3	24.7	10.2	26.9	3.3	3.9	0.4	3.5	2.8	<0.0001
Others/Unknown	34.7	16.2	14.3	21.5	2.6	3.7	0	1.9	4.9	<0.0001
Socioeconomic Status										
Lowest	34.2	18.3	13.5	22.4	2.9	2.9	0.4	1.9	3.3	<0.0001
lower-middle	28.9	19.4	13.6	24.9	3.5	3.1	0.7	2.5	3.4	<0.0001
Middle	27	20.4	12.6	26.1	3.7	3.8	0.4	2.6	3.4	<0.0001
Higher-middle	24.9	21	12.5	26.7	3.9	3.8	0.5	3.6	2.9	<0.0001
Highest	21.3	22.2	10.9	28.4	4.3	4.7	0.7	4.4	3	<0.0001
Clinical Stage										
IIIA	15.5	10.1	7.8	28.2	9.9	12.1	1.2	11.6	3.4	<0.0001
IIIB	25	16.9	9.7	30	6.3	4.3	0.5	3.9	3.4	<0.0001
IV	30.3	23.6	14.4	24.2	1.7	1.5	0.4	0.8	3.1	<0.0001

Table 3

Analysis of trends in treatment over the study period. A. Entire cohort N= 34,016. B. Patients with Stage IIIA disease. C. Patients with Stage IIIB disease. D. Patients with Stage IV disease.

A. Entire Cohort

Treatment Group	Parameter estimate	P value
No treatment received	0.002	0.179
Chemo only	0.006	<.001
Radiation only	−0.002	0.011
Chemo + Radiation	0.001	0.125
Surgery only	−0.003	<.001
Chemo + Surgery	−0.002	0.021
Surgery + Radiation	−0.001	0.007
Surgery + Chemo + Radiation	−0.001	0.094
Unknown	−0.001	0.275

B. Patients with Stage IIIA disease

Treatment Group	Parameter estimate	P value
No treatment received	0.009	<.001
Chemo only	−0.002	0.368
Radiation only	−0.001	0.433
Chemo + Radiation	0.002	0.931
Surgery only	−0.002	0.341
Chemo + Surgery	−0.003	0.181
Surgery + Radiation	−0.001	0.262
Surgery + Chemo + Radiation	−0.002	0.391
Unknown	−0.001	0.343

C. Patients with Stage IIIB disease

Treatment Group	Parameter estimate	P value
No treatment received	−0.007	0.050
Chemo only	0.001	0.781
Radiation only	−0.001	0.373
Chemo + Radiation	0.027	0.022
Surgery only	−0.010	0.006
Chemo + Surgery	−0.004	0.062
Surgery + Radiation	−0.001	0.090
Surgery + Chemo + Radiation	−0.003	0.012
Unknown	−0.003	0.031

D. Patients with Stage IV disease

Treatment Group	Parameter estimate	P value
No treatment received	0.002	0.352
Chemo only	0.007	<.001
Radiation only	−0.003	0.018
Chemo + Radiation	−0.0004	0.645
Surgery only	−0.002	0.012
Chemo + Surgery	−0.001	<.001
Surgery + Radiation	−0.001	0.017
Surgery + Chemo + Radiation	−0.001	0.068
Unknown	−0.001	0.481

Table 4

Median Survival Time in Months for Stage IIIA, IIIB, and IV

	Median Survival Time (95% CI)		
	Stage IIIA	**Stage IIIB**	**Stage IV**
Chemo only	14.1 (12.7–15.3)	11.3 (10.4–12.4)	10.1 (9.6–10.4)
Chemo + Radiation	19.2 (17.9–20.5)	16.2 (15.2–17.4)	9.8 (9.4–10.1)
Surg + Chemo + Rad	39.6 (33.4–47.3)	32.9 (26.8–40.7)	25.5 (20.6–30.2)
Chemo + surgery	48.6 (42.6–55.3)	50.7 (37.8–63.3)	28 (25–33)
Surgery only	32.6 (29.1–38.5)	32.7 (24.4–45.7)	17.4 (12.9–25.6)
Surgery + Radiation	30.2 (22.4–36.4)	29.6 (19.6–50.9)	9.4 (6.4–11.8)
Rad only	10.8 (9.2–12.5)	7.3 (6.4–8.3)	3.2 (3.1–3.3)
No Treatment	4.9 (4.4–5.8)	2.8 (2.6–3.2)	1.9 (1.8–2.0)
Unknown	19.3 (14.9–23.6)	9.7 (7.9–12.2)	5.9 (4.8–7.2)

Table 5

Predictors of Overall Survival (Data not shown for Cancer-Specific Survival, available upon request). N= 31,992, patients with missing covariates or who were diagnosed at autopsy were excluded.

Overall Survival			
Predictor	**Hazard Ratio**	**95% Confidence Limits**	**P-value**
Treatment subgroup			
No Treatment	Ref		
Chemo only	0.385	(0.373–0.398)	<.0001
Rad only	0.199	(0.184–0.215)	<.0001
Chemo + Radiation	0.403	(0.389–0.417)	<.0001
Surgery only	0.759	(0.731–0.789)	<.0001
Chemo + surgery	0.221	(0.203–0.241)	<.0001
Surgery + Radiation	0.321	(0.272–0.378)	<.0001
Surg + Chemo + Rad	0.251	(0.232–.27)	<.0001
Unknown	0.49	(0.457–0.526)	<.0001
Age			
<65	Ref		
65–74	1.094	(1.063–1.126)	<.0001
75+	1.228	(1.192–1.265)	<.0001
Gender			
Male	1.215	(1.186–1.244)	<.0001
Female	Ref		
Race			
White	Ref		
Asian/Pacific Islander	0.724	(0.698–0.751)	<.0001
Hispanic	0.914	(0.88–0.95)	<.0001
Black	0.976	(0.936–1.019)	0.2676
Socioeconomic Status			
Highest	Ref		
Higher-middle	1.063	(1.023–1.104)	0.0017
Lowest	1.176	(1.129–1.226)	<.0001
Middle	1.085	(1.045–1.127)	<.0001
lower-middle	1.124	(1.082–1.169)	<.0001
Clinical Stage			
IIIA	Ref		
IIIB	1.168	(1.118–1.221)	<.0001
IV	1.809	(1.742–1.879)	<.0001
Histology			
Adenocarcinoma	Ref		

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Overall Survival			
Predictor	**Hazard Ratio**	**95% Confidence Limits**	**P-value**
Squamous Cell Carcinoma	1.074	(1.044–1.104)	<.0001
Tumor size			
≤20 mm	Ref		
>20–30 mm	1.065	(1.007–1.126)	0.0264
>30–50 mm	1.179	(1.122–1.239)	<.0001
>50–70 mm	1.382	(1.312–1.456)	<.0001
>70 mm	1.579	(1.506–1.656)	<.0001

Table 6

Predictors of Treatment Group. N= 32,789, patients with missing covariates were excluded.

	OR (95% Confidence Interval)			
	Chemo + Radiation vs No Treatment	**Chemo Only vs No Treatment**	**Radiation Only vs No Treatment**	**Any Surgery vs No Treatment**
Predictor				
Age (Ref <65)				
65–74	0.508 (0.471–0.547)	0.738 (0.681–0.799)	0.805 (0.732–0.885)	0.603 (0.545–0.667)
>75	0.189 (0.175–0.205)	0.397 (0.366–0.43)	0.665 (0.608–0.729)	0.232 (0.208–0.259)
Race (Ref = White)				
Asian/Pacific				
Islander	1.143 (1.041–1.256)	1.387 (1.262–1.525)	0.85 (0.754–0.957)	1.209 (1.065–1.373)
Hispanic	0.902 (0.817–0.994)	1.067 (0.965–1.179)	0.823 (0.732–0.926)	0.941 (0.82–1.08)
Black	0.826 (0.739–0.924)	0.962 (0.857–1.081)	0.88 (0.771–1.004)	0.659 (0.559–0.777)
Socioeconomic Status (Ref = Highest SES)				
Higher-middle	0.74 (0.668–0.819)	0.768 (0.691–0.853)	0.961 (0.848–1.09)	0.66 (0.579–0.752)
Middle	0.668 (0.604–0.739)	0.694 (0.625–0.771)	0.905 (0.799–1.025)	0.533 (0.467–0.608)
Lower-middle	0.562 (0.507–0.623)	0.599 (0.538–0.666)	0.904 (0.798–1.024)	0.431 (0.376–0.494)
Lowest	0.431 (0.386–0.481)	0.477 (0.426–0.534)	0.772 (0.677–0.88)	0.32 (0.275–0.371)
Sex (Ref= Female)				
Male	1.015 (0.954–1.081)	0.903 (0.846–0.963)	1.043 (0.968–1.124)	0.768 (0.705–0.836)
Clinical Stage (Ref = Stage IIIA)				
Stage IIIB	0.68 (0.567–0.718)	1.076 (0.932–1.241)	0.758 (0.646–0.889)	0.232 (0.204–0.263)
Stage IV	0.361 (0.328–0.398)	1.093 (0.971–1.231)	0.906 (0.796–1.03)	0.053 (0.047–0.059)
Year of Diagnosis (Ref = 2004)				
2005	0.94 (0.817–1.082)	0.923 (0.795–1.073)	0.955 (0.812–1.124)	0.994 (0.832–1.189)
2006	0.979 (0.853–1.124)	1.001 (0.864–1.16)	0.945 (0.804–1.111)	0.866 (0.723–1.038)
2007	0.938 (0.817–1.078)	1.057 (0.913–1.223)	0.899 (0.763–1.058)	0.895 (0.749–1.071)
2008	0.943 (0.822–1.082)	1.048 (0.906–1.211)	0.857 (0.729–1.009)	0.832 (0.695–0.997)
2009	1.016 (0.887–1.164)	1.137 (0.986–1.311)	0.967 (0.826–1.133)	0.846 (0.708–1.012)
2010	1.009 (0.883–1.153)	1.027 (0.892–1.182)	0.8 (0.683–0.938)	0.689 (0.575–0.826)
2011	1.064 (0.932–1.2150	1.18 (1.027–1.357)	0.907 (0.776–1.061)	0.623 (0.519–0.747)
2012	0.95 (0.833–1.083)	1.116 (0.973–1.28)	0.765 (0.653–0.895)	0.519 (0.433–0.624)