Thorac Res Pract. 2024; 25(4): 141-148 DOI: 10.5152/ThoracResPract.2024.23120

Original Article

Population-Based Analysis of Local Therapies for Large (>7 cm) Non-Small Cell Lung Cancer Tumors

Deven C. Patel[1,2], Hao He[1], Douglas Z. Liou[1], Paul J. Speicher[3], Mark F. Berry[1]

[1]Department of Cardiothoracic Surgery, Stanford University, Palo Alto, CA, USA
[2]Division of Thoracic Surgery, Department of Surgery, The Johns Hopkins Medical Institutions, Baltimore, MD, USA
[3]Department of Cardiothoracic Surgery, University of Alabama at Birmingham School of Medicine, Huntsville, AL, USA

Cite this article as: Patel DC, He H, Liou DZ, Speicher PJ, Berry MF. Population-based analysis of local therapies for large (>7 cm) non-small cell lung cancer tumors. *Thorac Res Pract.* 2024;25(4):141-148.

Abstract

OBJECTIVE: This study evaluated the impact of local treatment modalities in the management of large non-small cell lung cancer (NSCLC) tumors using a nationwide population-based dataset.

MATERIAL AND METHODS: Patients with NSCLC tumors >7 cm that were cN0-1M0 in the Surveillance, Epidemiology, and End Results (SEER) registry from 2010 to 2015 were stratified by local management strategy (surgery, radiation therapy, no local treatment) and evaluated using Kaplan–Meier survival analyses, Cox proportional-hazard methods, and propensity-matched analysis.

RESULTS: A total of 3156 patients were identified, of which 1580 (50.1%) underwent surgical resection, 920 (29.2%) received radiation only, 655 (20.7%) received no local treatment. Overall, the 5-year survival of patients undergoing surgical resection was 40.7%, compared to 14.7% and 5.3% for the radiation only and no local treatment groups, respectively ($P < .001$). Surgery with or without radiation continued to have an independent association with improved survival in multivariable analysis (HR 0.23, $P < .0001$). Other factors associated with improved survival included younger age, negative nodal disease, and chemotherapy use. In propensity-matched sub-analyses, 5-year survival remained significantly better after surgery alone compared to radiation alone (38.5% vs. 13.6%, $P < .001$), while survival after radiation alone was better than no local treatment, though both were largely poor (12.4% vs. 7.5%, $P < .001$).

CONCLUSIONS: Survival of patients with large NSCLC managed non-surgically is very poor. Despite the significant long-term survival benefit with surgical intervention, nearly half of the study cohort did not undergo surgery. Patients and clinicians can use these results to estimate specific potential benefits when considering possible treatment strategies for large NSCLC tumors.

KEYWORDS: Non-small cell lung cancer, large tumors, surgery, radiation therapy, survival, comparative effectiveness

Received: *November 11, 2023* ***Revision Requested:*** *January 23, 2024* ***Last Revision Received:*** *April 4, 2024*
Accepted: *April 18, 2024* ***Publication Date:*** *June 17, 2024*

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in the world, with nearly 1.76 million deaths annually.[1] Tumor size is an independent prognostic factor, and larger tumors are associated with worse survival.[2,3] Accordingly, each new iteration of the American Joint Committee on Cancer (AJCC) and International Association for the Study of Lung Cancer (IASLC) staging systems has placed a greater significance on size, specifically tumors larger than 7 cm.[4,5] The T status for a tumor larger than 7 cm was classified as T2 in the sixth edition, became T3 in the seventh edition, and is now T4 in the eighth edition.

Despite the increased recognition of the importance of tumor size on outcomes, objective data regarding the optimal management of large non-small cell lung cancer (NSCLC) tumors are generally lacking. Surgical resection and external beam radiation therapy are local treatment options, and generally combined with systemic chemotherapy, and some occasions used together as a trimodal treatment strategy. Although the risks of lung cancer resection have been well categorized and are generally well understood, the benefits of surgery relative to alternative treatments are not as well quantified, especially when considering that data from clinical trials or specialized centers may not be generalizable to all centers that treat lung cancer. Large tumors may require complex or extensive surgical resection, which clinicians or patients may avoid because of the associated perioperative risks.[6] This study was undertaken to examine treatment patterns in a nationwide population-based dataset with the primary goal of evaluating the impact of local management strategies on long-term survival for patients with NSCLC tumors >7 cm in size, and should provide objective data that can be used in the risk/benefit process of local treatment strategies, specifically surgery vs. definitive radiation when these patients are evaluated in the multidisciplinary setting.

MATERIAL AND METHODS

We conducted this retrospective secondary analysis using the Surveillance, Epidemiology, and End Results (SEER) database. Supported by the National Cancer Institute, the SEER program collects and publishes cancer incidence and survival data

Corresponding author: Mark F. Berry, e-mail: berry037@stanford.edu

from population-based cancer registries covering approximately 35% of the United States population.[7] Patients were identified using ICD-O-3 location codes for lung cancer (C34.0-C34.9) and appropriate SEER histology codes ranging from 8012 to 8576 for all possible NSCLC histologies.

Patients included in this study were those 18 years or older with NSCLC primary tumors of at least 7 cm diagnosed between 2010 and 2015. During the study period, the AJCC Cancer Staging Manual, 7th edition, classified tumors greater than 7 cm as T3. Accordingly, inclusion criteria for the current study consisted of patients with T3 tumors and size greater than 7 cm. Note, the eightedition AJCC Staging Manual, updated in 2016, has classified tumors greater than 7 cm as T4. Only patients with N0-1 disease were kept for analysis because surgery may not have a role in the setting of advanced nodal disease.[8] Of note, SEER reports TNM data using Collaborative Staging (CSv2), utilizing a combination of clinical and pathologic data to provide standardized staging and tumor size information across all SEER participants.[9] Patient age, sex, race, ethnicity, marital status, insurance status, and survival follow-up time were also extracted. Patients living longer than 7 years were right-censored. Survival data are recorded from the time of cancer diagnosis.

Our primary focus was to examine the impact of local therapies on survival for potentially resectable large NSCLCs (≥7 cm), with the caveat that chemotherapy is likely to be employed irrespective of the local treatment strategy utilized. Patients were stratified by local treatment approach (surgery with or without radiation, radiation without surgery, or no local treatment). In order to quantify factors that may have been important in the selection of local therapy, multivariable logistic regression was used to estimate predictors of surgical intervention in patients. The covariates entered in this model were those considered significant on univariate analyses, our clinical experience, and the existing literature. Unadjusted survival analyses, stratified by treatment approach, were performed using the Kaplan–Meier method. A multivariable Cox proportional hazards model was created to estimate the independent effect of local treatment modality on survival adjusted for other important patient and disease-related factors. Covariates in the Cox models included local therapy modality as well as age sex, race, marital status, insurance, N stage, tumor size (treated as continuous variable), histology, and receipt of chemotherapy.

Several additional analyses were performed to quantify the treatment and outcomes of patients with large tumors. Propensity-matched analysis was performed due to the likelihood that some patients selected for more aggressive therapy had better outcomes not only because of the therapy but also due to other unmeasured factors, such as better pulmonary function, higher functional status, and less comorbid conditions. Two propensity-matched sub-analyses were performed: comparing patients treated with surgical resection alone vs. radiation therapy alone, as well as radiation therapy alone vs. no local treatment. Propensity scores were calculated using a logistic regression model in which age, patient sex, marital status, insurance status, N stage, tumor size, and receipt of chemotherapy were included as predictors. Propensity scores between the 2 groups were matched 1:1 through a Greedy algorithm with a caliper of 0.2 standard deviations. After matching, Kaplan–Meier analysis was used to compare long-term survival. To better understand which patients may be more likely to benefit from surgical resection, a Cox proportional hazards model was created to estimate predictors of survival in the subset of patients who underwent surgery, utilizing the same covariates as above, as well as the usage of induction or adjuvant radiation therapy. Given the limited granularity regarding patient comorbidities and functional status in the SEER database, a survival sub-analysis using patients younger than 60 years, married, and insured was created to include patients more likely to tolerate aggressive cancer treatment based on age and socioeconomic support.

Main Points

- Over the past several years, there has been increased recognition for the importance of non-small cell lung cancer (NSCLC) tumor size on outcomes. Accordingly, the American Joint Committee on Cancer (AJCC) has placed greater weight on tumors larger than 7 cm; however, despite a greater appreciation for tumor size on outcomes, the optimal local treatment strategy for these large tumors is generally lacking.
- In this national analysis, we explore the current treatment trends and long-term outcomes for patients with NSCLC tumors >7 cm. This study demonstrates grim survival for patients with large NSCLC tumors managed non-surgically.
- Despite proven benefits, nearly half of the study cohort opted against surgery, influenced by factors like age, race, and insurance status.
- Treatment must be carefully considered for all patients based on their individual characteristics, but higher operative risks may be acceptable in the management of very large NSCLC tumors considering the potential survival benefit of surgery over other treatment options.

Statistical Analysis

Missing data were rare and handled with case-wise deletion. Univariate comparisons were conducted using Pearson's chi-square tests or Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables. A *P*-value < .05 was used to indicate statistical significance for all comparisons and analyses. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc. NC, USA).

Ethics Committee Approval

This study was considered exempt by the Institutional Review Board at Stanford University.

RESULTS

A total of 3156 patients diagnosed with NSCLC tumors of at least 7 cm between 2010 and 2015 were identified for inclusion in this study (Supplementary Figure 1). Of these, 1580 (50.1%) underwent surgical resection with or without radiation, 920 (29.2%) received radiation therapy only, and 655 (20.7%) received no local treatment. The baseline demographic characteristics of these patients are shown in Table 1,

Table 1. Baseline Patient Characteristics of the Entire Cohort and Stratified by Local Management Strategy

Patient Characteristic	Total (n = 3156)	Surgical Resection ± Radiation (n = 1580)	Radiation Only (n = 920)	No Local Treatment, (n = 655)	*P*
Age (years)					<.001
18-50	147	104 (6.6%)	31 (3.4%)	12 (1.8%)	
51-64	963	540 (34.2%)	265 (28.8%)	158 (24.1%)	
65-74	1088	563 (35.6%)	314 (34.1%)	211 (32.2%)	
75+	958	374 (23.7%)	310 (33.7%)	274 (41.8%)	
Sex					.116
Male	1972	987 (62.4%)	595 (64.7%)	390 (59.5%)	
Female	1184	594 (37.6%)	325 (35.3%)	265 (40.5%)	
Race					<.001
White	2540	1305 (82.5%)	710 (77.2%)	526 (80.3%)	
Black	384	156 (9.9%)	148 (16.1%)	80 (12.2%)	
Others	231	120 (7.6%)	62 (6.7%)	49 (7.5%)	
Marital status					<.001
Single	1357	581 (36.8%)	420 (45.7%)	356 (54.4%)	
Married	1659	936 (59.2%)	455 (49.5%)	268 (40.9%)	
Unknown	140	64 (4.1%)	45 (4.9%)	31 (4.7%)	
Insurance					.074
Uninsured	91	37 (2.3%)	33 (3.6%)	21 (3.2%)	
Insured	3024	1530 (96.8%)	873 (94.9%)	621 (94.8%)	
Unknown	41	14 (0.9%)	14 (1.5%)	13 (2.0%)	
Tumor size (>7 cm)					
Median (IQR)	8.5	8.5 (7.5, 10)	8.3 (7.6, 9.6)	8.4 (7.6, 10)	.008
Nodal stage					.001
N0	2297	1128 (72.3%)	657 (71.4%)	512 (79.1%)	
N1	830	432 (27.7%)	263 (28.6%)	135 (20.9%)	
Chemotherapy	1730	886 (56.0%)	667 (72.5%)	177 (27.0%)	<.001
Extent of surgical resection					NA
Sublobar	–	41 (2.6%)	–	–	
Lobectomy	–	1264 (80.6%)	–	–	
Pneumonectomy	–	276 (17.5%)	–	–	
Histology					<.001
Adenocarcinoma	1229	811 (51.3%)	228 (24.8%)	190 (29.0%)	
Squamous cell carcinoma	1362	566 (35.8%)	480 (52.2%)	316 (48.2%)	
Large cell neuroendocrine carcinoma	85	58 (3.7%)	17 (1.9%)	10 (1.5%)	
Adenosquamous carcinoma	55	38 (2.4%)	13 (1.4%)	4 (0.6%)	
Other non-small cell histology	425	108 (6.8%)	182 (19.8%)	135 (20.6%)	
Lymph node examined					<.001
No	1441	48 (3.0%)	786 (85.4%)	607 (92.7%)	
Yes	1702	1532 (96.9%)	125 (13.6%)	45 (6.9%)	
Unknown/NA	13	1 (0.1%)	9 (1.0%)	3 (0.5%)	
Lymph node positive					<.001
Negative	1274	1129 (71.4%)	108 (11.7%)	37 (5.7%)	
Positive	426	401 (25.5%)	17 (1.9%)	8 (1.2%)	
Not-examined/unknown/NA	1456	51 (3.2%)	795 (86.4%)	610 (93.1%)	

both for the entire cohort and stratified by management strategy. The median tumor size for the study cohort was 8.5 cm. The majority of patients across groups were male and white, with node-negative disease. Older patients were more likely to receive no local treatment for their large tumors. The majority of patients undergoing a local treatment strategy also had chemotherapy, whereas only a minority of patients who received no local treatment underwent systemic chemotherapy (surgery: 56.0% vs. radiation: 72.5% vs. no local treatment: 27.0%, $P < .001$). Among patients undergoing surgery, the vast majority underwent lobectomy (80.6%). Increasing age, Black race, squamous cell carcinoma histology, and chemotherapy use were predictors of non-surgical treatment in a multivariable logistic regression model (Figure 1). Patient sex and absolute tumor size did not have a significant association with the use of surgery, but married and insured patients were more likely to have surgery. Among patients receiving both surgery and radiation therapy, the majority of surgical patients received radiation in the postoperative setting (Supplementary Table 4).

Kaplan–Meier survival curves, stratified by treatment approach, are shown in Figure 2. The overall 5-year survival of patients undergoing surgery with or without radiation therapy was 40.7%, compared to 14.7% for the radiation therapy group, and 5.3% for the no local treatment group ($P < .001$). The results of the Cox proportional hazards survival model, adjusted for treatment strategy and available baseline and tumor characteristics, are shown in Table 2. Overall, local treatment was associated with improved survival compared to patients receiving no local treatment. However, surgery with or without radiation had the largest association with survival (HR 0.24, $P < .001$). Increasing patient age and N1 disease were associated with worse survival. Conversely, female

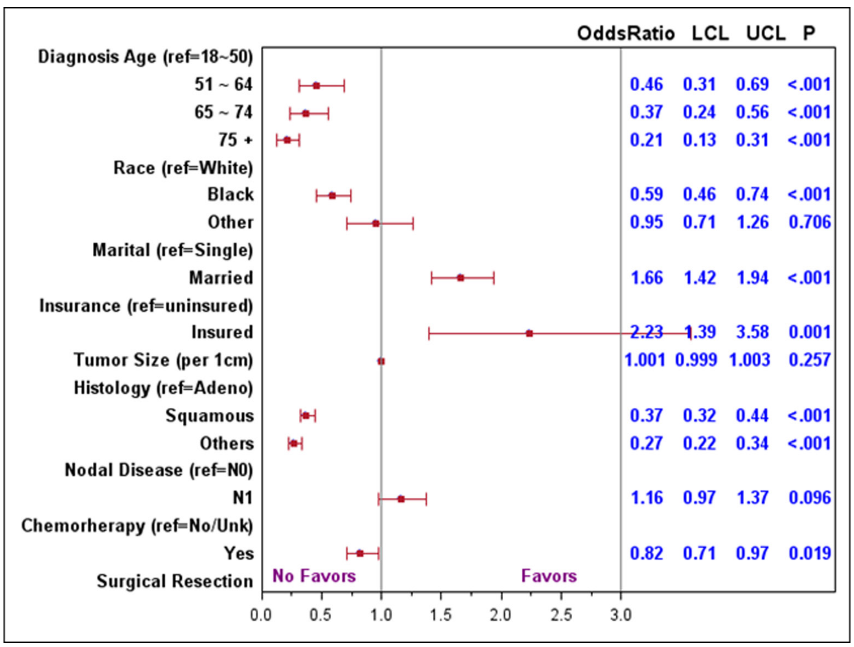


Figure 1. Predictors of surgical intervention among patients with large (at least 7 cm) NSCLC tumors.

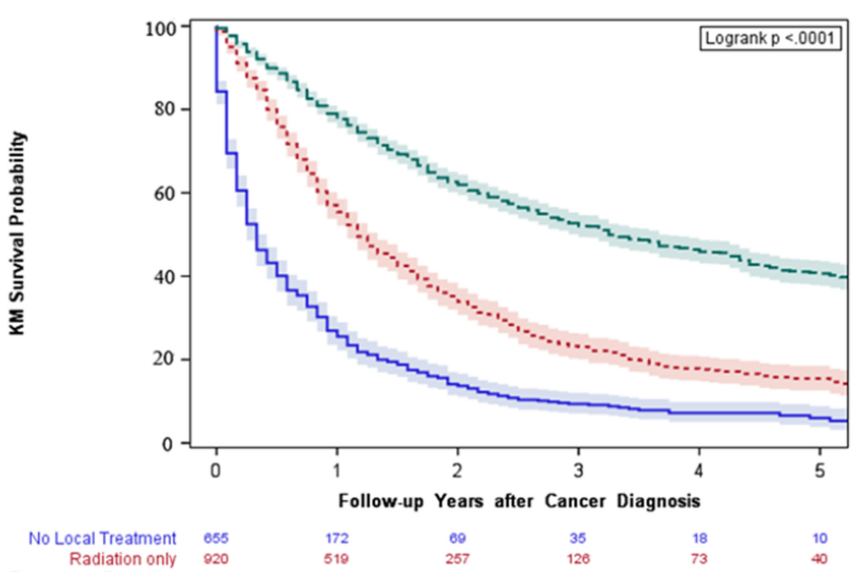


Figure 2. Kaplan–Meier survival estimates for patients with large NSCLC, stratified by treatment approach.

Table 2. Results of Cox Proportional Hazard Modeling Showing Adjusted Risk of Death in the Entire Cohort of Patients with Large NSCLC Tumors

Predictors	Hazard Ratio	95% CI		P
		Lower	Upper	
Local treatment approach				
No local treatment	*Ref*			
Surgical resection ± radiation	0.24	0.21	0.27	<.001
Radiation only	0.52	0.46	0.59	<.001
Age (yrs)				
18-50	Ref			
51-64	1.36	1.04	1.77	.023
65-74	1.58	1.21	2.06	.001
75+	1.82	1.39	2.38	<.001
Sex				
Male	Ref			
Female	0.84	0.77	0.92	<.001
Race				
White	Ref			
Black	0.91	0.80	1.06	.240
Others	0.74	0.62	0.89	.001
Marital status				
Single	Ref			
Married	0.91	0.83	0.99	.043
Insurance				
Uninsured	Ref			
Insured	1.06	0.80	1.41	.691
Tumor size (>7 cm)				
Per 1 cm increase	1.00	0.99	1.00	.482
Nodal stage				
N0	Ref			
N1	1.25	1.13	1.38	<.001
Histology				
Adenocarcinoma	Ref			
Squamous cell carcinoma	1.42	1.28	1.57	<.001
Others	1.39	1.23	1.58	<.001
Chemotherapy				
No/unknown	Ref			
Yes	0.55	0.50	0.61	<.001

sex, marriage, and receipt of chemotherapy all predicted improved survival. As shown in Supplementary Table 2, short-term survival rates between surgery ± radiation therapy were comparable to the radiation-only group (1 month: 97.6% vs. 95.0%, respectively).

The results of the propensity-matched sub-analysis comparing surgical resection alone vs. radiation therapy alone were consistent with the results of the main analysis. In a total of 567 matched pairs, there were no differences in patient characteristics (Supplementary Table 1). Patients who underwent surgery alone had significantly better 5-year survival than matched patients who had radiation therapy alone (38.5% vs. 13.6%, $P < .001$) (Figure 3). In the propensity-matched analysis of the subset of patients not undergoing surgery, patients undergoing radiation therapy had a substantially higher survival estimate at 1 year compared to matched patients undergoing no local treatment (51.3% vs. 33.4%). At 5 years, patients treated with radiation had a statistically significantly improvement in overall survival compared to those not undergoing treatment, though the prognosis of both groups were generally poor (12.4% vs. 7.5%, $P < .001$) (Figure 4). In a sub-analysis using patients younger than 60 years, married, and insured, short-term survival between radiation only and surgery ± radiation groups was very similar (Supplementary Table 3); however, surgery continued to demonstrate a significant survival benefit in long-term analysis (Supplementary Figure 2).

The overall 30-day and 90-day mortality after surgery was 0.51% and 4.31%, respectively. Parsed by the extent of resection, the 30-day/90-day mortality rates were as follows: sublobar resection: 0.00%/9.76%, lobar resection: 0.40%/2.62%, and pneumonectomy: 1.09%/11.31%. Table 3 demonstrates the Cox proportional hazards model using only patients who had undergone surgical resection. Surgical patients who received radiation therapy demonstrated worse survival (HR 1.34, $P = .002$). Female sex, receipt of chemotherapy, and patients who were married were associated with a survival benefit. Increasing age and N1 disease predicted worse survival. Although the Cox model showed a qualitatively, though not statistically significant difference in survival between lobar resections and pneumonectomy, survival between these extents of resections were compared and shown to be slightly different (5-year OS 41.0% for lobectomy vs. 39.1% for pneumonectomy, $P = .004$) (Supplementary Figure 3).

DISCUSSION

Large NSCLC tumors pose a challenging clinical dilemma that requires thoughtful consideration into the variety of treatment strategies. In this study, we sought to investigate whether an aggressive localized treatment strategy involving surgery would confer a long-term survival benefit that would potentially justify the perioperative risks. Using the nationwide SEER registry, we demonstrate that patients with potentially resectable NSCLC of at least 7 cm in size realize a substantial long-term survival benefit following surgical resection compared with non-operative locoregional therapy. Patients who underwent surgery were generally younger, insured, married, and less likely to have undergone systemic chemotherapy. Independent benefits to surgery were found in both multivariable survival analysis and propensity-matched analysis. Further, in a sub-analysis examining all surgical patients, the addition of radiation therapy was associated with worse survival, while chemotherapy demonstrated a survival advantage. While our results also demonstrate that radiation therapy alone confers a marginal survival benefit compared to no local treatment, outcomes when surgery is not utilized are poor.

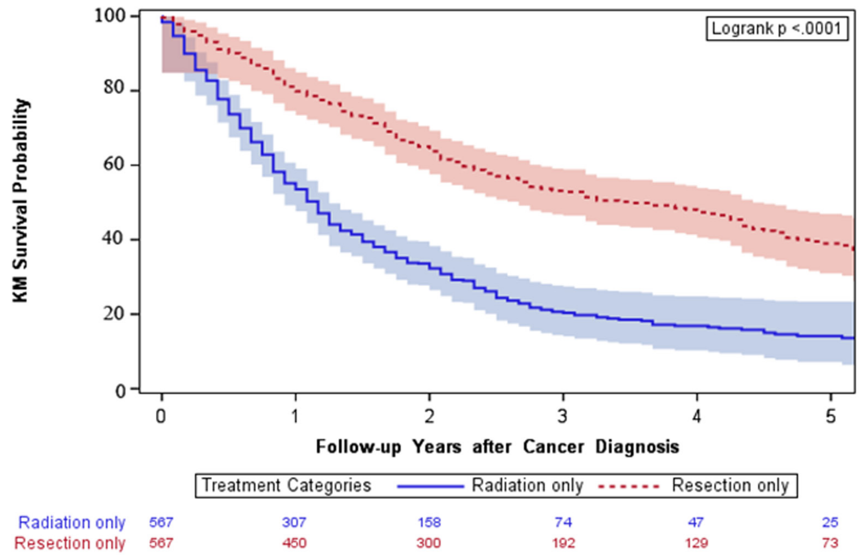


Figure 3. Kaplan–Meier survival estimates for propensity matched patients undergoing surgical resection alone vs. radiation alone for large NSCLC tumors.

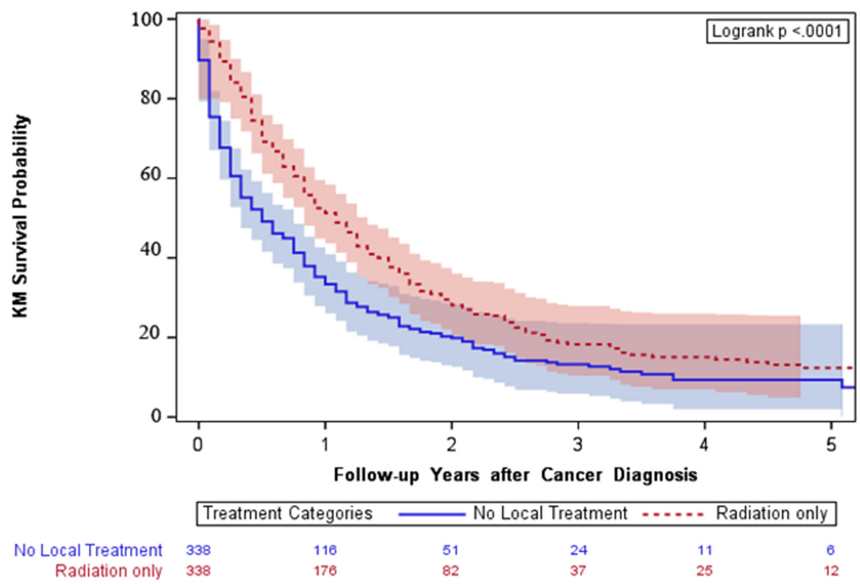


Figure 4. Kaplan–Meier survival estimates for propensity matched patients undergoing radiation alone vs. no local treatment for large NSCLC.

Despite the significant long-term survival benefit of surgical intervention, nearly 50% of the study cohort did not undergo surgery for tumors ≥7 cm in this population-based analysis. The strongest predictor for not receiving surgery was increasing age, particularly patients older than 75 years. Consistent with the existing literature in health disparities, patients of black race and those who were uninsured were less likely to undergo surgery in the current study.[10,11] For these reasons, we speculate that elderly and other patients with poor access to care or limited social support were not considered surgical candidates and possibly did not even receive a surgical evaluation. Although deferring surgery may have been appropriate in many patients, the very poor outcomes seen when surgery is not utilized suggest that all patients should at least undergo careful consideration of surgery. Patients who are turned down for surgery may benefit from a second opinion from a high-volume or more specialized center, where the risks of surgery may be less, and should at the least be discussed at a multi-disciplinary conference where both the relative risks and potential benefits are carefully considered. This current study provides quantitative data from a large cohort of patients on the benefits and alternative management options for the informed consent process prior to surgery.

The poor outcomes following non-surgical therapy, as demonstrated in this study, can likely be attributed to a number of factors related to tumor size. Generally, as tumor volume increases in many cancers, neoplastic cells outgrow their blood supply, and the subsequent hypoxia can have substantial undesirable effects on radiation penetration.[12,13] Radiation therapy alone can also lead to substantial morbidity. Effective therapy resulting in substantial tumor death can lead to a large necrotic mass in the chest cavity, the sequelae of which include abscess and infection, bronchopulmonary fistulae, and impaired pulmonary mechanics. While surgical resection also carries substantial morbidity when managing these large tumors, the short-term risks associated with non-operative therapy cannot be discounted when determining optimal

Table 3. Results of Cox Proportional Hazard Modeling Showing Adjusted Risk of Death in the Subset of Patients Who Had Surgical Resection of Large NSCLC Tumors

Predictors	Hazard Ratio	95% CI		*P*
		Lower	Upper	
Local treatment approach				
Surgical resection without radiation	*Ref*			
Surgical resection with radiation	1.34	1.11	1.61	.002
Age (yrs)				
18-40	*Ref*			
41-64	1.36	0.95	1.94	.093
65-74	1.76	1.23	2.52	.002
75+	2.08	1.43	3.01	<.001
Sex				
Male	*Ref*			
Female	0.78	0.67	0.91	.001
Race				
White	*Ref*			
Black	1.10	0.87	1.39	.422
Others	0.73	0.54	0.99	.044
Marital status				
Single	*Ref*			
Married	0.97	0.83	1.12	.658
Insurance				
Uninsured	*Ref*			
Insured	1.20	0.71	2.04	.490
Tumor size (>7 cm)				
Per 1 cm increase	1.00	0.99	1.00	.589
Nodal Stage				
N0	*Ref*			
N1	1.48	1.26	1.74	<.001
Histology				
Adenocarcinoma	*Ref*			
Squamous cell carcinoma	1.21	1.03	1.41	.019
Others	1.32	1.06	1.63	.013
Extent of surgical resection				
Sublobar	*Ref*			
Lobectomy	0.85	0.56	1.30	.460
Pneumonectomy	1.05	0.67	1.66	.820
Chemotherapy				
No/unknown	*Ref*			
Yes	0.61	0.52	0.72	<.001

management for patients. In this study, short-term survival of radiation therapy alone demonstrated slightly lower survival than surgery ± radiation therapy, suggesting potential selection bias, possibly secondary to pre-existing medical comorbidities and functional status—which cannot be fully captured by the SEER database. However, the short-term mortality for both local treatment strategies were overall very low for the first few months. Additionally, in a sub-analysis using a presumably healthier patient subset with socioeconomic support, surgery continued to demonstrate a significant long-term survival benefit. Thus, suggesting a patient's general medical conditions and functional status alone are unlikely to explain the observed benefit of surgery. Further, the short-term harm of surgery may be overstated, and morbidity from radiation may be underappreciated.

The importance of tumor size as a prognostic factor for NSCLC is well recognized.[2,3] Indeed, reasonable long-term outcomes after surgery for locally advanced tumors have been demonstrated before, including in studies used to revise T staging definitions.[4] However, objective data that compare treatment options and therefore could guide therapeutic decision are generally limited.[14-16] In a National Cancer Database study evaluating patients with >7 cm, hilar lymph node-positive NSCLC from 1999 to 2005, local therapy in the form of surgery alone demonstrated no significant difference in survival compared to patients receiving definitive chemoradiotherapy.[17] In the aforementioned study, only when chemotherapy was combined with surgery did 5-year overall survival improve compared to non-surgical treatment groups and those receiving no treatment. In the current study, surgical resection was associated with a substantial survival advantage in comparison to other non-surgical treatment strategies, even when adjusting for nodal disease and the use of chemotherapy.

The use of the SEER dataset for this analysis allowed the construction of a large cohort of patients across a wide range of institutions, enabling more generalizable results compared to studies that predominantly involve high-volume or specialized centers, and therefore provide strong data on a relatively uncommon clinical scenario. Nonetheless, this SEER analysis does have limitations, which are lessened but not eliminated by the use of propensity matching. Our results are likely limited by a notable selection bias, as treatment allocation to surgery or radiation therapy, as well as the extent of surgical resection, may be confounded by unmeasured variables including pre-existing medical comorbidities, functional status, and high risk tumor features not captured by the dataset. Although all patients included in this study are potentially resectable based on TNM staging criteria, it is likely that some of the radiation therapy patients were deemed unfit for surgery due to disease that would present a particularly challenging technical resection or invasion of adjacent organs. The results of this study are limited by the lack of granular radiation therapy data and the inability to distinguish between palliative intent and curative intent, which could underestimate the potential curative benefit of radiation. Outside of a clinical trial, delineating the impact of systemic therapy is challenging due to the potential variety of agents, doses, sequence, and number of treatments that can be used, and further compounded by the very limited granularity regarding chemotherapy in the SEER dataset. The absence of resection margin data precludes this study from commenting on the impact of an R1 or R2 resection. Residual disease was likely a major impetus for adjuvant radiation therapy and aligned with the worse survival seen in this study for patients undergoing surgery and radiation compared to surgery alone. The lack of information on the specific mediastinal staging used to determine the nodal stage precludes us from commenting on this important aspect of the diagnostics used to determine the appropriate treatment strategy. The study period in this study was used to maximize long-term follow up, however, more modern outcomes may have provided a greater understanding of adjuvant strategies and the use of targeted therapies or immunotherapy. Finally, as SEER reports tumor size using best available clinical or pathologic information, the accuracy of the tumor size is expected to be more exact in patients undergoing upfront surgery compared to patients undergoing radiation therapy in which size was based on clinical information.

For patients with potentially resectable NSCLC tumors of 7 cm or greater, long-term outcomes after surgery are considerably better than non-surgical treatment strategies. Although radiation therapy confers marginal survival benefit compared to no local treatment, outcomes remain dismal, particularly when compared to surgical intervention. These results, which quantify the potential benefits of local treatment options, are useful to both patients and clinicians when weighing management options for large cancers. Treatment must be carefully considered for all patients based on their individual characteristics, but higher operative risks may be acceptable in the management of very large NSCLC tumors considering the potential survival benefit of surgery over other treatment options.

Ethics Committee Approval: Ethics Committee/Institutional Review Board of Stanford University exempted this study as SEER data is publicly available and de-identified.

Peer-review: Externally peer-reviewed.

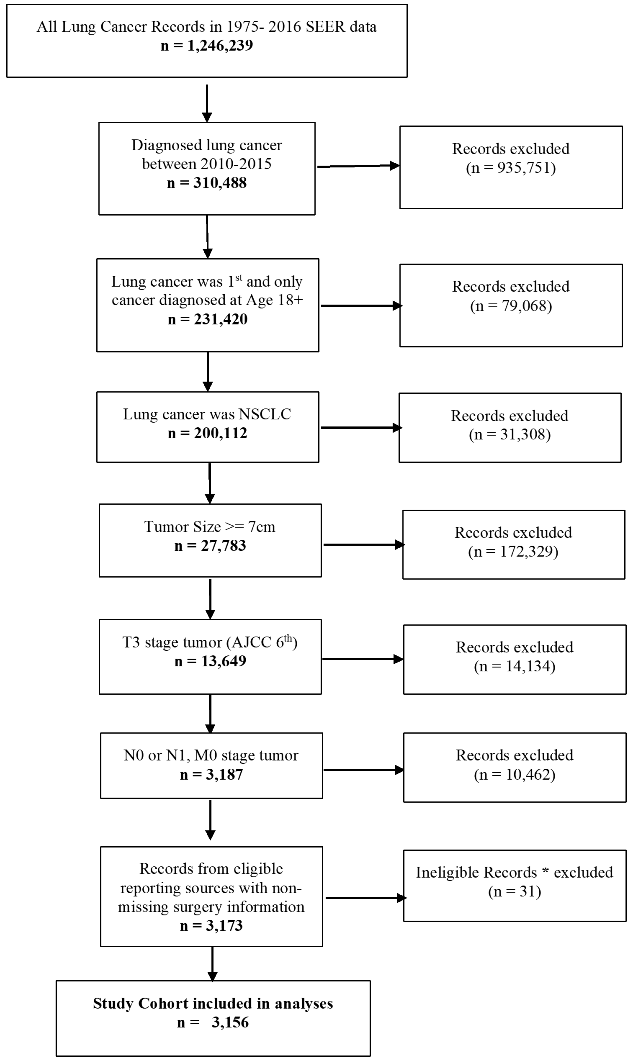
Author Contributions: Concept – P.J.S., M.F.B.; Design – D.C.P., H.H., D.Z.L., P.J.S., M.F.B.; Supervision – M.F.B.; Resource – D.C.P., H.H., D.Z.L., P.J.S., M.F.B.; Materials – D.C.P., H.H., D.Z.L., P.J.S., M.F.B.; Data Collection and/or Processing – D.C.P., H.H., D.Z.L., P.J.S., M.F.B.; Analysis and/or Interpretation – D.C.P., H.H., D.Z.L., P.J.S., M.F.B.; Literature Search – D.C.P., H.H., D.Z.L., P.J.S., M.F.B.; Writing – D.C.P., H.H., D.Z.L., P.J.S., M.F.B.; Critical Review – D.C.P., H.H., D.Z.L., P.J.S., M.F.B.

Declaration of Interests: The authors declare that they have no competing interests.

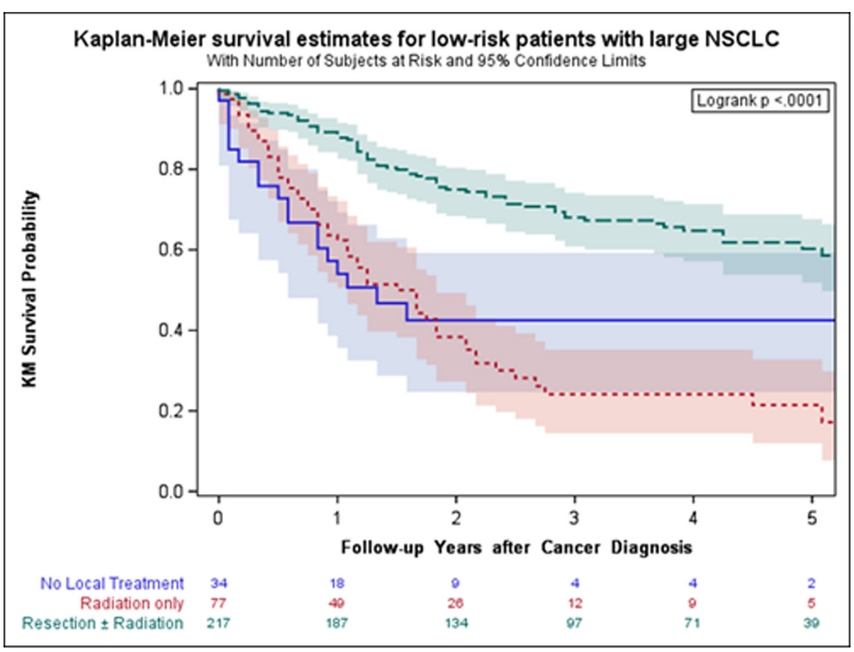
Funding: This study received no funding.

REFERENCES

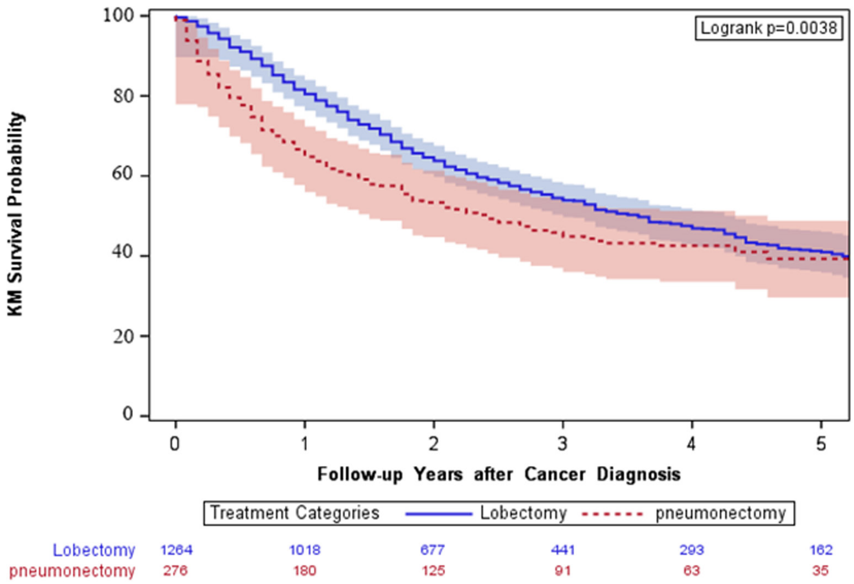
1. World Health Organization. Cancer. https://www.who.int/newsroom/fact-sheets/detail/cancer. Accessed December 24, 2020.
2. Zhang J, Gold KA, Lin HY, et al. Relationship between tumor size and survival in non–small-cell lung cancer (NSCLC): an analysis of the surveillance, epidemiology, and end results (SEER) registry. *J Thorac Oncol*. 2015;10(4):682-690. [CrossRef]
3. Cangır AK, Kutlay H, Akal M, Güngör A, Özdemir N, Akay H. Prognostic value of tumor size in non-small cell lung cancer larger than five centimeters in diameter. *Lung Cancer*. 2004;46(3):325-331. [CrossRef]
4. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC lung cancer staging project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2015;10(7):990-1003. [CrossRef]
5. Abdel-Rahman O. Validation of the prognostic value of new sub-stages within the AJCC 8th edition of non-small cell lung cancer. *Clin Transl Oncol*. 8th ed. 2017;19(11):1414-1420. [CrossRef]
6. Vossler JD, Abdul-Ghani A, Tsai PI, Morris PT. Outcomes of anatomic lung resection for cancer are better when performed by cardiothoracic surgeons. *Ann Thorac Surg*. 2021;111(3):1004-1011. [CrossRef]
7. Institute NC. Overview of the SEER Program. Available at: https://seer.cancer.gov/about/overview.html. Accessed March 24, 2021.
8. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374(9687):379-386. [CrossRef]
9. Adjusted AJCC 6th ed. T, N, M, and Stage. *Surveillance, Epidemiology, and End Results Program Collaborative Stage (CS) 2004-2015*. Available at: https://seer.cancer.gov/seerstat/variables/seer/ajcc-stage/6th/. Accessed June 24, 2022.
10. Lutfi W, Martinez-Meehan D, Sultan I, et al. Racial disparities in local therapy for early stage non-small-cell lung cancer. *J Surg Oncol*. 2020;122(8):1815-1820. [CrossRef]
11. Patel DC, He H, Berry MF, et al. Cancer diagnoses and survival rise as 65-year-olds become Medicare-eligible. *Cancer*. 2021;127(13):2302-2310. [CrossRef]
12. Barker HE, Paget JTE, Khan AA, Harrington KJ. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. *Nat Rev Cancer*. 2015;15(7):409-425. [CrossRef]
13. Dewhirst MW. Relationships between cycling hypoxia, HIF-1, angiogenesis and oxidative stress. *Radiat Res*. 2009;172(6):653-665. [CrossRef]
14. Chambers A, Routledge T, Billè A, Scarci M. Does surgery have a role in T4N0 and T4N1 lung cancer? *Interact Cardiovasc Thorac Surg*. 2010;11(4):473-479. [CrossRef]
15. Sun BJ, Bhandari P, Yang C-FJ, et al. Induction therapy is not associated with improved survival in large cT4 N0 non-small cell lung cancers. *Ann Thorac Surg*. 2021.
16. Yamanashi K, Menju T, Hamaji M, et al. Prognostic factors related to postoperative survival in the newly classified clinical T4 lung cancer. *Eur J Cardiothorac Surg*. 2020;57(4):754-761. [CrossRef]
17. Moreno AC, Morgensztern D, Boffa DJ, et al. Treating locally advanced disease: an analysis of very large, hilar lymph node positive non-small cell lung cancer using the National Cancer Data Base. *Ann Thorac Surg*. 2014;97(4):1149-1155. [CrossRef]



Supplementary Figure 1. Consolidated standards of reporting trails (CONSORT) diagram outlining patient selection. *Ineligible records include following sources: Laboratory Only (hospital-affiliated or independent); Nursing/Convalescent Home/Hospice; Autopsy Only; Death Certificate Only.



Supplementary Figure 2. Kaplan-Meier survival estimates for low-risk subgroup (age < 60, married, and insured), stratified by treatment approach.



Supplementary Figure 3. Kaplan-Meier survival estimates for patients with large NSCLC, stratified by extent of surgical resection, lobectomy versus pneumonectomy.

Supplementary Table 1. Baseline Patient Characteristics of Propensity-score Matched Patients Receiving Surgical Resection only Versus Radiation Therapy Only

Patient characteristic	Surgical resection only (n = 567)	Radiation therapy only (n = 567)	*P*
Age (years)			.563
18-50	25 (4.1%)	24 (4.2%)	
51-64	195 (34.4%)	178 (31.4%)	
65-74	191 (33.7%)	213 (37.6%)	
75+	156 (27.5%)	152 (26.8%)	
Sex			.459
Male	354 (62.4%)	367 (64.7%)	
Female	213 (37.6%)	200 (35.3%)	
Race			.560
White	455 (80.3%)	467 (82.4%)	
Black	64 (11.3%)	61 (10.8%)	
Others	48 (8.5%)	39 (6.9%)	
Marital status			.831
Single	247 (43.6%)	240 (42.3%)	
Married	303 (53.4%)	307 (54.1%)	
Unknown	17 (3.0%)	20 (3.5%)	
Insurance			.561
Uninsured	14 (2.5%)	16 (2.8%)	
Insured	550 (97.0%)	545 (96.1%)	
Unknown	3 (0.5%)	6 (1.1%)	
Tumor Size (>7 cm)			
Median [IQR]	8.2 [7.5, 9.8]	8.4 [7.6, 10.0]	.615
Nodal Stage			.405
N0	383 (67.6%)	397 (70.0%)	
N1	184 (32.5%)	170 (30.0%)	
Chemotherapy	379 (66.8%)	375 (66.1%)	.850

Supplementary Table 2. Short-term Survival Rates for Resection ± Radiation and Radiation Only Groups in the Study Cohort

	Months after Cancer Diagnosis					
Treatment Groups	**1 month**	**2 months**	**3 months**	**4 months**	**5 months**	**6 months**
Radiation only	95.0%/46	91.1%/82	87.5%/115	85.7%/141	79.9%/184	75.9%/222
Resection ± Radiation	97.6%/37	95.6%/68	93.7%/98	92.1%/125	89.9%/159	88.5%/179

*Short-term survival rates/cumulative death.

Supplementary Table 3. Sub-analysis, Short-Term Survival Rates for Resection ± Radiation and Radiation only Groups in Low-risk Subgroup (age < 60, insured and Married Patients)

	Months after Cancer Diagnosis					
Treatment Groups	**1 month**	**2 months**	**3 months**	**4 months**	**5 months**	**6 months**
Radiation only	97.4%/2	93.5%/5	89.6%/8	87.0%/10	83.1%/13	77.9%/17
Resection ± Radiation	98.6%/3	97.7%/5	96.3%/8	94.4%/12	94.0%/13	93.5%/14

*Short-term survival rates/cumulative death.

Supplementary Table 4. Radiation Sequence with Surgery

Sequence	Frequency	Percent
Radiation before surgery	89	2.82
Radiation after surgery	287	9.09
Radiation both before and after surgery	8	0.25
Intraoperative radiation with other radiation given before or after surgery	1	0.03
Surgery before and after radiation	3	0.10
No radiation and/or surgery as defined above	2768	87.71