Title
Surgical and Non-Surgical Outcomes for Patients with Non-Small Cell Lung Cancer

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Publication Date
2020

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA,
IRVINE

Surgical and Non-Surgical Outcomes for Patients with Non-Small Cell Lung Cancer

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

Yajie Yin

Dissertation Committee:
Professor Sherrie Kaplan, Chair
Professor Sheldon Greenfield
Assistant Professor Jeremy P Harris

2020

DEDICATION

To

my parents, family, committees, and friends

in recognition of their support

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LIST OF ABBREVIATIONS

NSCLC	Non-small cell lung cancer
SCLC	Small-cell lung cancer
SBRT	Stereotactic body radiation
EGFR	Epidermal growth factor receptor
TK	Tyrosine kinases
ASTRO	American Society for Therapeutic Radiation Oncology
CRT	Chemo-radiotherapy
Lob	Lobectomy
SEER	Surveillance, Epidemiology, and End Results
NCI	National Cancer Institute
NIH	National Institutes of Health
SD	Standard Deviation
KM	Kaplan-Meier
MVA	Multivariate analyses
OS	Overall survival
CSS	Cancer-specific survival
HR	Hazard Ratio
BED	Biologically equivalent dose

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ACKNOWLEDGEMENTS

I would like to express the deep appreciation to my committee chair, Professor Sherrie Kaplan, who has the attitude and the substance of a genius: she continually and convincingly conveyed a spirit of science in regard to research, and an enthusiasm for the "underlying structures" had lasting. Without her guidance and support this dissertation would not have been possible.

I would like to thank my committee members, Professor Sheldon Greenfield and Professor Jeremy P Harris, whose work demonstrated to me that pursuing the modern technology persistently should always transcend academia and provide a quest for our times.

In addition, a thank you to Professor Bae-Jump and Professor Chunxiao Zhou of University of North Carolina at Chapel Hill, who introduced me to the Translational Medicine, and offered me professional training.

Also, a thank you to my classmates, Nyles, Chimezie. Thanks to my friends, Tiyia, Sarah, Yao, and Chad, and to the lovely dog, Burrito.

Thanks, God, for bringing me to UCI. "Let there be light."

ABSTRACT OF THE THESIS

Survival of Stereotactic Body Radiation Therapy vs. Lobectomy in Patients with Non-small Cell Lung Cancer

by

Yajie Yin

Master of Biomedical and Translational Science

University of California, Irvine, 2020

Professor Sherrie Kaplan, Chair

Objective: Determine the clinical effectiveness of definitive treatment for non-small cell lung cancer (NSCLC) and perform a comparative effectiveness study of the different techniques, between surgical resection of lobectomy, radiation therapy (RT), and stereotactic body radiation (SBRT).

Patients and Methods: This study used data from the SEER Program, with 20,889 patients with Stage IA to IIIC. NSCLC The inclusion criteria were any patient identified from SEER from 2014 to 2016, over 18 years old.

Chi-squared tests were used to evaluate the differences in dichotomous variables between the treatment groups. Unadjusted Kaplan-Meier methods were used to estimate overall survival and cancer-specific survival, and we used log-rank tests to evaluate the differences in time-to-event outcomes. Two-sided p values were used, and significance level was set at 0.05. Adjusted Cox regression models assumed proportional hazards.

Results: A total of 13,760 NSCLC patients with clinical stage IA to IIIC treated with lobectomy were compared with 7,129 patients treated with radiotherapy. Adjusted multivariable Cox proportional hazards models found lobectomy to be associated with significantly better outcomes compared to radiotherapy for both early-stage (hazard ratio, T1N0, 0.31, P<.001) and advanced-stage (hazard ratio, T2N2, 0.43, P<.001). Additionally, patients undergoing lobectomy had improved mean cancer-specific survival for stages IA to IIIC.

Conclusion: Among NSCLC patients with clinical stage IA to IIIC in the SEER Database, surgical resection with lobectomy is associated with significantly improved outcomes compared to definitive radiation. Radiation for early stage disease (SBRT) or combined with chemotherapy for locally advanced-stage disease remains a good treatment option. However, when medical comorbidities and tumor characteristics permit, surgical resection should be pursued. For patients with unresectable disease, this study supports the consideration of chemoradiation as a tool to enable downstaging to achieve surgical resection.

I. INTRODUCTION

1. Background

Lung cancer remains one of the most common malignancies (only second to nonmelanoma skin cancer) and the leading cause of cancer-related death in the United States in past years. Worldwide, lung cancer is also the second most prevalent cancer diagnosed in the UK with poor prognosis after prostate cancer in males and breast cancer in females. [1] Same in Canada, Lung cancer is being the second most diagnosed cancer with the leading cause of cancer death. Long-term survival in these patients is poor, and the overall 5-year survival rate was 15%. Among newly diagnosed NSCLC patients, approximately 20% to 30% of stage I patients was medically inoperable due to comorbidities. [2] These patients taking radiation therapy delivered with the outcome of local 3-year recurrence rates as high as 29% to 57%, and overall survival rates are as low as 20% to 50%. [2] There are two main types of lung cancer, small-cell lung cancer (SCLC) and none small-cell lung cancer (NSCLC), which accounts for approximately 85% of all lung cancer. The expectation of lung cancer deaths was 142,670 to occur in 2019 nationwide, accounting for about 27% of all cancer deaths in the United States. [3]

The pathological diagnosis depends on the histological characteristics, including SCLS and NSCLC, according to the 2015 World Health Organization classification. With apparent morphological features of adenocarcinoma or squamous cell carcinoma, the routine immunohistochemistry or immunocytochemistry analysis is not required. Neuroendocrine features may be considered as SCLC or NSCLC (most likely large cell neuroendocrine carcinoma). Inapparent morphological evidence for adenocarcinoma or squamous cell

carcinoma is classified into non-small cell lung cancer (NSCLC, not otherwise specified [NOS], NSCLC NOS). NSCLC NOS can be further subdivided depending on immunocytochemical or immunohistochemical analysis, mucin staining, or molecular data. According to the researched of familial clustering or aggregation in the past decades, lung cancer has suggested a hereditary base to disease development, including the increased risk in the carriers of TP53 germline sequence variations, additional genes (ERBB2, MET, BRAF, KRAS, and RET), the germline epidermal growth factor receptor (EGFR), and cigarettes smoking. [4]

The most consistent and gold standard treatment is surgical resection for non-small cell lung cancer patients in diagnosis, staging, curative treatment, and palliative care, among which lobectomy is regrading as the current criterion standard of pulmonary resection. Nearly 70% of NSCLC patients were with locally advanced or metastatic disease at the beginning of diagnosis. [5] Given the limitation of curative-intent surgery in locally advanced or metastatic stage, chemotherapy is another standard of care (National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Non–Small Cell Lung Cancer. V. 2.2010). [6] Adjuvant chemotherapy is a recommended benefit for NSCLC patients with stage IIA through IIIA. Additionally, the option of treatment for NSCLC patients depends on the molecular features of tumors somehow. Targeted therapy is an alternative method-specific on the cell-signaling and regulatory pathways involved with the overexpression or gene sequence variation in lung cancer, such as alterations in receptor tyrosine kinases (TKs), EGFR, and angiogenesis pathways, apoptosis, cell cycle control, *etc.* Stereotactic body radiotherapy (SBRT) techniques are used to treat small

tumors (T1-2, N0, M0), performing the fixation, ultraprecise treatment planning, RT directed to gross disease alone, and high doses per fraction.

The American Society for Therapeutic Radiation Oncology (ASTRO) regarded the Stereotactic body radiotherapy (SBRT) as the standard of care for early-stage medically inoperable NSCLC patients. The guidelines strongly recommended the conventional RT for altered fractionation for central tumors and surgery over SBRT with standard-risk in early-stage NSCLC. ASTRO also conditionally approved the SBRT as salvage therapy after prior radiation for tumors >5 cm, following a pneumonectomy, T3 tumors invading the chest wall in synchronous multiple primary lung cancer. [7] SBRT uses high doses of radiation delivered to a highly precise target. Recently, studies evaluating the efficacy and safety of SBRT for early-stage NSCLC patients have been increasingly focused on medically inoperable patients, regarding that SBRT might be an alternative to surgery for operable patients with early-stage NSCLC (T1-2N0).

For locally advanced-stage NSCLC (stage III), the optimal treatment regimen remains debated. In general, surgical expertise guides therapy. In 8th TMN staging, the definition of stage IIIA/B differentiated a little from the past. Previous trials evaluated the utility of trimodality therapy, including neoadjuvant chemoradiation followed by surgery, neoadjuvant chemotherapy followed by surgery, surgery followed by chemotherapy, surgery followed by chemoradiation, and definative chemoradiation. [8] Compared to the surgery group alone, the postoperative chemotherapy with cisplatin and UFT improved the survival of NSCLC patients in stage IIIA. The cisplatin reduced about 11% relative mortality, and UFT led to an approximate 17%, respectively. Similarly, the rate of 5-year

survival increased by 4% relatively in IIIA patients, which also reduced the local recurrence for those patients. [9]

2. Trial Review

NCCN recommends lobectomy as standard therapy for operable, stage I NSCLC patients, which includes mediastinal node sampling. As experience with SBRT has grown, local control rates have been in the range of 90% for patients with medically inoperable tumors. [7] As local control rates improved, the new clinical question became whether radiation therapy would result in similar outcomes to lobectomy.

Recently, three clinical trials were conducted to compare SABR to surgery for patients with early-stage NSCLC. All 3 randomized trials were phase 3; the STARS trial [NCT00840749], the ROSEL trial [NCT00687986], and the ACOSOG Z4099 trial [NCT01336894]. [10] Unfortunately, they were all closed early due to slow accrual. In STARS, NSCLC patients were randomly automatically assigned in an equal ratio with randomized four blocks to receiving the intervention, stratified by site, TNM stage, tumor size, under the Merge randomization system. In ROSEL, eligible participants were stratified by the health care institute, histology, and WHO status, assigning in a ratio of 1:1 with another randomization system, TENALEAS. NSCLC patients were randomly assigned to receive operable lobectomy and dissection of the hilar lymph nodes. In both trials, all patients in the lobectomy group also underwent dissection of mediastinal lymph nodes.

There was a grouped analysis of the patients included in the STARS and ROSEL trials. Together, the two randomized trials enrolled a total of 58 patients, 31 were treated with SBRT and 27 with surgery. There were no statistically significant differences in multiple

covariates, such as age, sex, WHO performance status, histology, TNM stage, or tumor location between the two intervention groups. All stage I NSCLC patients were regarded as medically operable for lobectomy. Sixteen patients from the STARS trial received 54 Gy in three fractions because of peripherally located lesions, and the other three patients with central lesions received 50 Gy in four fractions. In the ROSEL trial, six patients received 54 Gy in three 18 Gy fractions within 5–8 days, and another five operated 60 Gy at five 12 Gy fractions over 10–14 days. [11] [12] Median follow-up for the SBRT patients was 40.2 months (IQR 23.0–47.3), while the median survival was 35.4 months (IQR 18.9–40.7) in the surgery group. The combination of the estimated overall survival at one year was 100% (95% CI 100–100) in the SBRT group and 88% (95% CI 77–100) in the surgery group, while the estimation of three years was 95% (95% CI 85–100) and 79% (95% CI 64–97), respectively. [13] Overall survival was significantly different with a p-value of 0.037, HR as 0.14 [95% CI 0.017–1.190]. Similarly, overall survival outcomes from the STARS trial data alone suggested a statistically significant difference with a p-value equal to 0.0067. [13]

To date, the publication on the Lancet Oncol is the first report of phase 3 data to compare SABR with surgery among operable patients, which indicated SBRT with better tolerance and better overall survival compared to surgery for operable stage I NSCLC patients. Similar clinical trials are ongoing in Japan, JCOG 0403 as a single-arm phase II study. There is also a larger phase 3 trial being conducted at the VA that is expected to better accrue and better address this question (VALOR study), although that trial is ongoing and not expected to be completed for a number of years. Given the limitation of the small sample size and short follow-up, the above conclusions have been interpreted

cautiously and have not resulted in SABR becoming the standard of care or recommended modality by the NCCN or ASTRO.

3. **Lobectomy**

In 1995, lobectomy was recognized as the gold standard for early-stage NSCLC patients as compared to smaller surgeries known collectively as sub-lobectomies. The rationale was that there are larger margins with a lobectomy and intralobar lymph nodes are removed, which results in more accurate pathologic staging. The 3-year overall survival rate after open lobectomy was about 82%, and the 5-year was approximately to be 66%. In the comparison between sublobar resection and the lobectomy cohort, the surgical margin positivity was also significantly difference between lobectomy and the sublobar group, with the result of 2.5% vs. 6.6%, ($p = 0.003$). Similar OS probability appeared among lobectomy and sublobar group, 61.7% vs. 55.6%. Sublobar related to a significantly increased risk of recurrence, meanwhile with the shorter median time to recurrence (17.7 months) compared to the lobectomy cohort (21.0 months). [14]

Given there are many medically inoperable NSCLC patients with lung function that is too poor to have a lobectomy, the debate about the role of sub-lobar for small peripheral tumors remains. The National Cancer Database analyzed the 4-year trends of treatment among early-stage NSCLC patients until 2012, indicating the rate of lobectomy was 50% in 2012. The Japanese clinical trial JCOG 0802 compared the outcome of lobectomy and the segmentectomy from 2009 to 2014, the result without significant difference between the two groups. [15] Improved surgical techniques, including with robotic surgery, helped improved outcomes after lobectomies, including operative time, blood loss, conversions

rates, R0 resection, hospitalization stay, and postoperative pain. The 30-day and 90-day mortality rates indicate improved quality of lobectomy with robotic surgery. However, robotic lobectomy suffers some disadvantages as well, considering the operational cost and efficiency. [16]

4. **Stereotactic Body Radiation (SBRT)**

SBRT differs from conventional radiation therapy based on the higher doses of 10 to 34 Gy per fraction over 1-5 fractions, while the conventional radiation gives 1.5 to 2 Gy per fraction over 25-35 fractions. Multiple SBRT systems have been used in the clinic, such as the robotic linear accelerator CyberKnife, TomoTherapy, and the MRI-cobalt linac ViewRay™, although by far the most popular technique is gantry-based linear accelerator. The dose delivered is key to the high local control rates seen with SABR in lung cancer. The biologically equivalent dose (BED) is a critical factor in understanding how SBRT can result in improved local control compared to conventional radiation therapy. [17] Decreased pulmonary function and an acute event of pneumonitis are the most common concerns with SBRT. Other severe complications higher than grade 3 occasionally occur, such as fibrotic change, chest wall toxicity, chest wall pain, rib fractures, and esophagitis, etc. In that way, SBRT has a much higher BED, which contributes to a better local tumor control as well as potentially higher toxicity. [18]

The current NSCLC study (RTOG 0236 & JCOG 0403) demonstrated that the distant recurrence would be regarded as a limitation among patients treated with SBRT. The rate of distant recurrence was approximately 25%, developed more frequently in stage T2 compared to T1, and there was a higher recurrence rate among non-squamous tumors than

squamous, 31% vs. 6%. [19] Therefore, some physicians have recommended combination SABR with systemic therapy to reduce the recurrence rate effectively for those NSCLC patients at high risk. The SEER database does not specify radiation modality (SABR versus conventional fractionation), and so for this study radiation therapy included beam radiation, conventional fractionation, and SBRT.

5. Treatment Options for Stage III Disease

The optimal treatment of locally advanced stage IIIA-N2 NSCLC remains on the debate, because of the heterogeneity of the disease's presentation and comorbidities, and the insufficient studies. It was apparent that concurrent chemotherapy and radiotherapy benefited more than the sequential combination in patients. The European randomized trial 0841 compared the unresectable patients with stage IIIA-N2 disease, receiving chemotherapy followed by either surgery or radiotherapy. The OS was approximately 15% in both groups, with no significant difference. [20] In the Intergroup/RTOG study, operable patients with stage IIIA-N2 received chemotherapy concurrently with radiotherapy showed no difference in the primary endpoint. In summary, it recommended the surgery followed by adjuvant therapy or concurrent CRT followed by surgery for operable patients with stage IIIA-N2. For inoperable patients, concurrent chemoradiotherapy implied to be the first option.

II. METHODS

1. Research Aim

The goal of this project is to determine the clinical effectiveness of definitive treatment for non-small cell lung cancer and perform a comparative effectiveness study of the different techniques. The current gold standard of care for early-stage lung cancer is surgical resection. For inoperable patients who are not candidates for surgery due to medical comorbidities, radiation is a reliable option when delivered via stereotactic body radiation (SBRT) technique. As SBRT techniques continue to improve, it hypothesized for some patients that there might be equipoise between surgery and radiation. Currently, only one small prospective analysis has been conducted, which was a pooled analysis of 2 randomized trials in phase 3. That study indicates the improved survival for patients treated with SBRT, but due to limitations in that study, it has not changed the practice nationwide. The extensive database studies available have shown that in general, surgery results in improved outcomes, but patient-specific comorbidity data about performance status and smoking status was not known for these analyses.

2. Database and Sample

This study created a database provided from Surveillance, Epidemiology, and End Results (SEER) Program in the National Cancer Institute (NCI) under the National Institutes of Health (NIH). The SEER Research Data Agreement form was signed to access the SEER data, and the approval was released by SEER.

As a retrospective observational study, the sample size depended on the available cohort, 20,889 patients. Inclusion and exclusion criteria are applied to that cohort to select

the study sample. The inclusive criteria were any patient identified in SEER from 2014 to 2016 with NSCLC, and whose age at diagnosis was over 18 years old. The patient should have no other kind of primary malignancies, whose clinic stage was from the IA to IIIC. According to the 8th of the TNM classification of NSCLC, the subsets of T1N0 belongs to stage IA, T2aN0 as Stage IB, T2bN0 as Stage IIA. It groups the T3N0 and T2N1 as Stage IIB, T4N0, T4N1, and T1-2N2 combined as Stage IIIA. Given the similar intervention strategy of Stage IIIB and IIIC, this study grouped them as a subset.

Table 1. The 8th of TNM Classification of NSCLC

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC

Figure 1. Treatment Schema for Early-Stage Patients

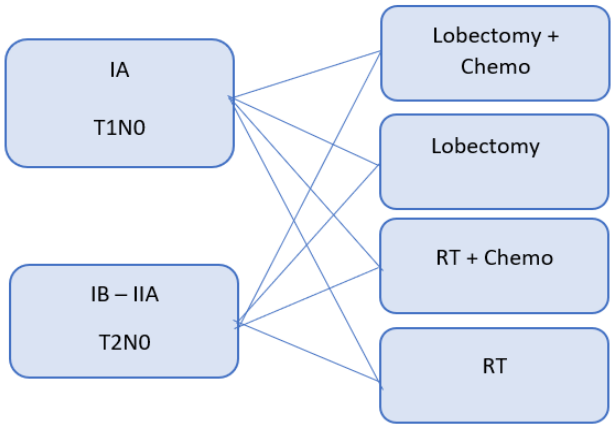
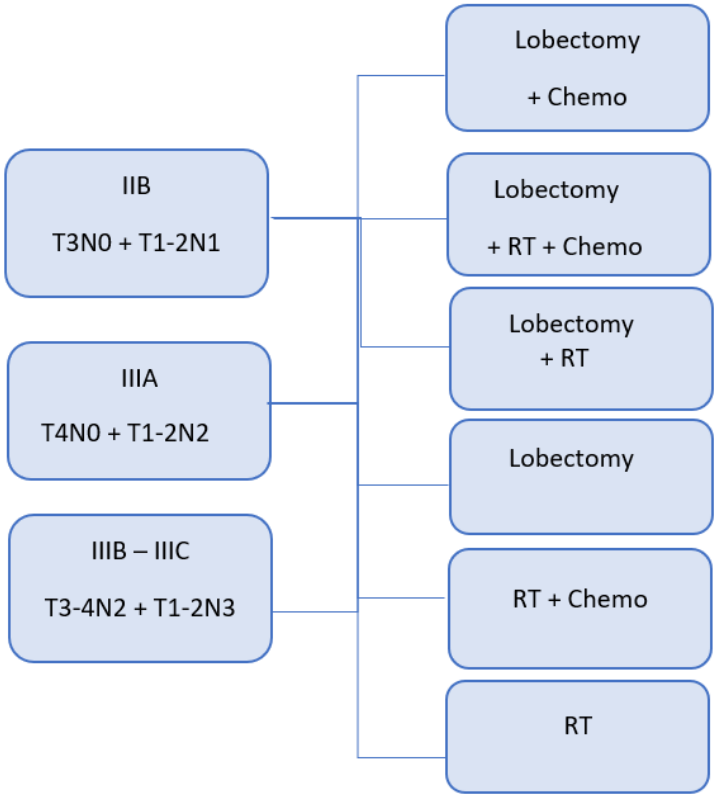


Figure 2. Treatment Schema for Locally Advanced-Stage Patients



3. **Statistical Design**

Data covariates considered included the year at diagnosis, sex, age, race (White, Black, and Others), tumor site, tumor size, laterality, grade, histology, clinical T stage, and treatment strategy (lobectomy, radiation). The dataset also supplemented other elements, such as health insurance status, urban/rural status, median income, and the education level, county / ZIP code/region. Summary statistics were provided with frequency count and percentage for categorical variables, mean, Standard Deviation (SD), median, and range for continuous variables. The chi-squared test evaluated the difference in a dichotomous variable between two the lobectomy and SBRT group. In this study, the unadjusted Kaplan-Meier method estimated overall survival and the cancer-specific survival and used log-rank

tests to evaluate the differences in time-to-event outcomes between the lobectomy and SBRT group with two-sided p values. The Kaplan-Meier computed the difference between the combo intervention with/out chemotherapy in each group. Adjusted Cox regression models anticipated the hazard ratio between the lobectomy group and the RT group. Stratified data estimated the correlation of risk factors in the cohort under the same stage, such as histological category, age group, and sex. The dataset was computed via SEERstat, and all analyses were performed by SPSS 25.0, with an alpha level of 0.05.

III. RESULTS

We identified 20,889 patients treated with Lobectomy or RT for stage IA to stage IIIC NSCLC between 2014 and 2016. Overall, the majority of tumors were laboratory proven with the rest clinically diagnosed. The description tables displayed the result of with each stage, in both lobectomy (Lob) and RT groups, along with the demographic characters of the entire cohort. Mean (SD) overall survival for the overall cohort of each stage was listed below with a 5-year cutoff point. The median follow-up might be limited shown as blank when the median was not reached. Several independent predictors of outcome were noted with the multivariate Cox (MVA) regression analysis, including age, sex, race, grade, histology, chemotherapy, and insurance type in the adjusted model.

1. Stage IA

Table 2. Descriptive Statistics Comparing Patients Undergoing Surgery vs. RT with Adjusted COX Proportional Hazards - Stage IA

IA, T1N0 Covariate	Lobectomy N (%)	RT N (%)	p	HR (95% CI)	P
	1429	5403			
Age			<0.001		
<50	238 (4.4)	2 (0.1)		1	0.001
50-59	985 (18.2)	79 (5.5)		1.00 (0.30-3.36)	0.998
60-69	2059 (38.1)	361 (25.3)		1.21 (0.38-3.87)	0.752
70-79	1759 (32.6)	572 (40.0)		2.03 (0.64-6.49)	0.232
>=80	362 (6.7)	415 (29.0)		1.93 (0.59-6.31)	0.279
Race			<0.001		
White	4448 (82.8)	1213 (85.0)		1	0.568
Black	462 (8.6)	137 (9.6)		0.92 (0.60-1.39)	0.679
Others	460 (8.6)	77 (5.4)		0.76 (0.44-1.30)	0.315
Sex			0.005		
Male	2199 (40.7)	640 (44.8)		1.59 (1.26-2.00)	<0.001
Female	3204 (59.3)	789 (55.2)		1.00	

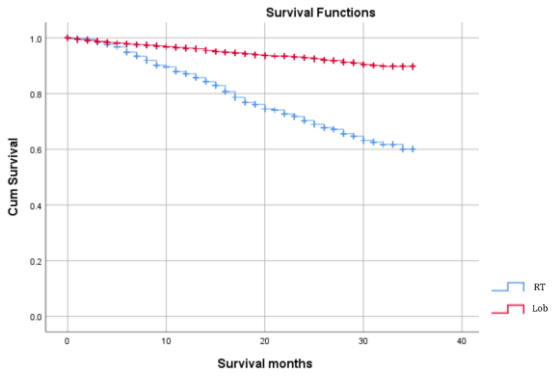
Grade			<0.001		
I	1548 (28.7)	280 (19.6)		1.00	<0.001
II	2604 (48.2)	578 (40.4)		2.30 (1.52-3.50)	<0.001
III	1192 (22.1)	559 (39.1)		3.45 (2.24-5.30)	<0.001
Undifferentiated	59 (1.1)	12 (0.8)		3.78 (1.35-10.63)	0.012
Histology			<0.001		
Adenocarcinoma	4196 (77.7)	772 (54.0)		1.00	0.622
Squamous	1072 (19.8)	572 (40.0)		1.13 (0.88-1.46)	00.343
Carcinoid	63 (1.2)	13 (0.9)		1.61 (0.74-3.51)	0.234
NOS	43 (0.8)	68 (4.8)		1.29 (0.74-2.26)	0.370
Others	29 (0.5)	4 (0.3)		0.67 (0.92-4.79)	0.686
Chemotherapy			<0.001		
No	5336 (98.8)	1354 (94.8)		1.00	
Yes	67 (1.2)	75 (5.2)		2.12 (1.37-3.29)	0.001
Insurance			0.238		
Insured	1245 (87.1)	4674 (86.5)			0.495
Medicaid	163 (11.4)	608 (11.3)		0.56 (0.25-1.27)	0.167
Uninsured	11 (0.8)	48 (0.9)		0.52 (0.21-1.26)	0.148
Unknown	10 (0.7)	73 (1.4)		0.76 (1.88-3.05)	0.695

Table 3. Unadjusted OS and CSS Stratified by Treatment – Stage IA

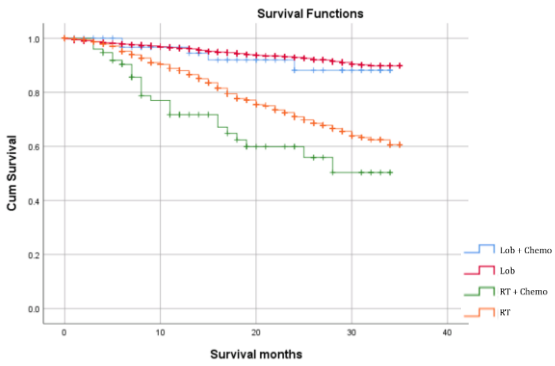
		Overall Survival				Cancer-Specific Survival			
Treatment	#N	Mean (SD)	95% CI	Median	95% CI	Mean (SD)	95% CI	Median	95% CI
Lobectomy	5336	33.13 (0.11)	32.92-33.35			34.03 (0.08)	33.87-34.19		
Lobectomy + Chemo	67	31.75 (0.96)	29.87-33.63			32.19 (0.87)	30.49-33.89		
RT	1354	28.22 (0.36)	27.51-28.93			30.89 (0.32)	30.27-31.51		
RT + Chemo	75	23.73 (1.59)	20.62-26.84			25.66 (1.56)	22.59-28.72		

Figure 3. Unadjusted Kaplan Meier Curves OS (A) and CSS (B) Stratified by Treatment type.

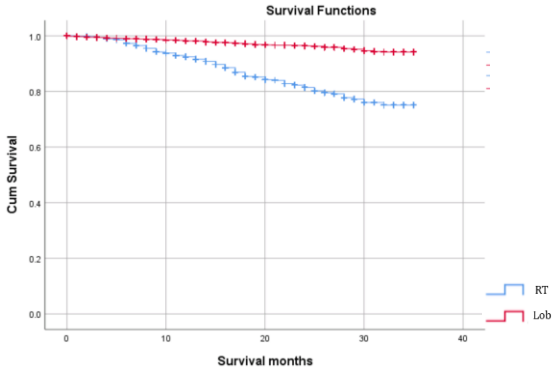
Adjusted COX Proportional Hazards (C) – Stage IA



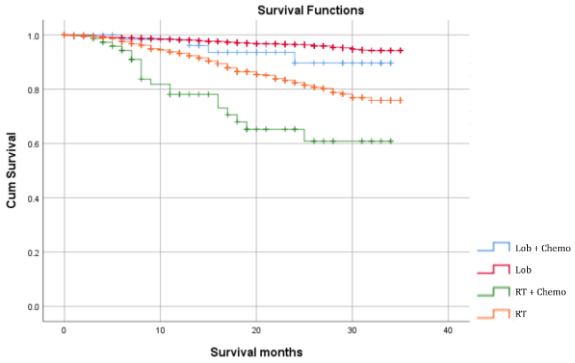
A1



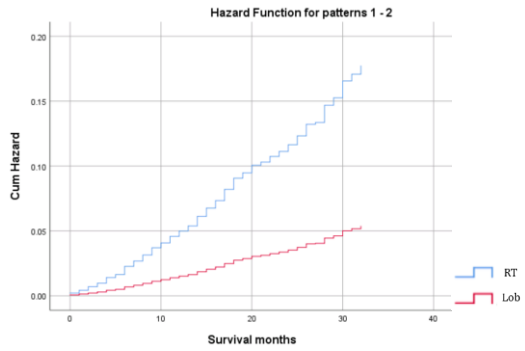
A2



B1



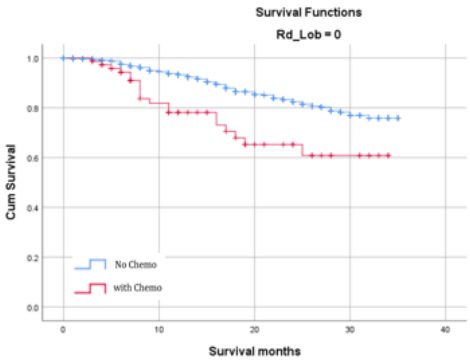
B2



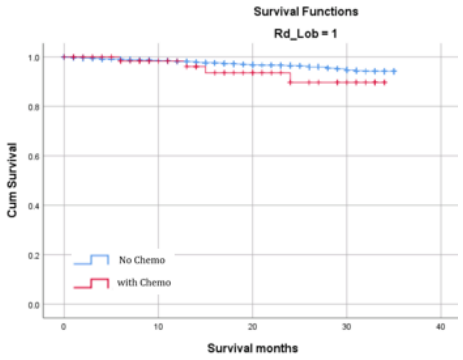
C

Fig 3. OS (A1, A2) and CSS (B1, B2) for unadjusted Lobectomy and RT cohorts, all with $p < 0.001$. In Adjusted COX Proportional Hazards (C), HR=3.30, $p < 0.001$.

Figure 4. Unadjusted Kaplan Meier Curves of Chemotherapy with CSS Stratified by Undergoing Lobectomy – Stage IA



A RT+/- Chemo, p < 0.001



B Lob+/-Chemo, p=0.190

Table 4. CSS of The Outcome-Related Variables – Stage IA

IA, T1N0		Cancer-specific survival			
Covariate	Mean (SD)	95% CI	Median	95% CI	#N
Age					p<0.001
<50	34.44 (0.32)	33.82-35.07			240
50-59	34.21 (0.17)	33.88-34.53			1064
60-69	33.82 (0.13)	33.57-34.08			2420
70-79	32.73 (0.18)	32.38-33.08			2331
>=80	32.16 (0.35)	31.47-32.84			777
Sex					p<0.001
Male	32.76 (0.17)	32.44-33.08			2839
Female	33,74 (0.11)	33.53-33.95			3993
Grade					p<0.001
I	34.42 (0.11)	34.21-34.64			1828
II	33.51 (0.13)	33.26-33.77			3182
III	31.93 (0.24)	31.46-32.40			1751
Undifferentiated	31.61 (1.44)	28.80-34.42			71
Chemotherapy					p<0.001
No	33.42 (0.09)	33.25-33.60			6690
Yes	28.85 (00.96)	26.98-30.73			142

Mean (SD) follow-up for patients was 33.13 (0.11) months in the Lobectomy group and 28.22 (0.36)months in the RT group in stage IA. Pooled estimated cancer-specific survival

(CSS) in surgery group alone vs. RT alone were [34.03 (0.08), 95% CI 33.87-34.19] and 30.89 (0.32) [95% CI 30.27-31.51]. There was a statistically significant difference in CSS between the two strategies (log-rank $p < 0.001$; HR = 3.30). The difference in CSS between with/out chemotherapy in RT group was significant ($p < 0.001$). OS was improved up to 5 months in lobectomy group versus the RT group. Multivariable contributed significant difference in CSS shown in Table 4.

2. Stage IB-IIA

Table 5. Descriptive Statistics Comparing Patients Undergoing Surgery vs. RT with Adjusted COX Proportional Hazards - Stage IB-IIA

IB-IIA, T2N0 Covariate	Lobectomy N (%)	RT N (%)	p	HR (95% CI)	P
	4964	1183			
Age			<0.001		
<50	212 (4.3)	8 (0.7)		1.00	<0.001
50-59	794 (16.0)	91 (7.7)		0.88 (0.47-1.65)	0.681
60-69	1730 (34.9)	251 (21.2)		1.07 (0.59-1.93)	0.832
70-79	1750 (35.3)	429 (36.3)		1.38 (0.76-2.48)	0.290
>=80	478 (9.6)	404 (34.2)		1.86 (1.02-3.41)	0.044
Race			<0.001		
White	452 (82.0)	986 (83.4)		1.00	0.033
Black	453 (9.2)	133 (11.3)		0.70 (0.52-0.95)	0.024
Others	434 (8.8)	63 (5.3)		1.18 (0.88-1.57)	0.268
Sex			0.005		
Male	2431 (49.0)	633 (53.5)		1.23 (1.05-1.44)	0.01
Female	2533 (51.0)	550 (46.5)		1.00	
Grade			<0.001		
I	737 (14.8)	138 (11.7)		1.00	<0.001
II	2388 (48.1)	481 (40.7)		1.46 (1.07-1.99)	0.017
III	1747 (35.2)	551 (46.6)		2.25 (1.65-3.06)	<0.001
Undifferentiated	92 (1.9)	13 (1.1)		1.46 (0.72-2.95)	0.295
Histology			<0.001		
Adenocarcinoma	3369 (67.9)	484 (40.9)		1.00	
Squamous	1412 (28.4)	629 (53.2)		1.21 (1.01-1.44)	0.002
Carcinoid	71 (1.4)	7 (0.6)		2.50 (1.43-4.37)	0.001

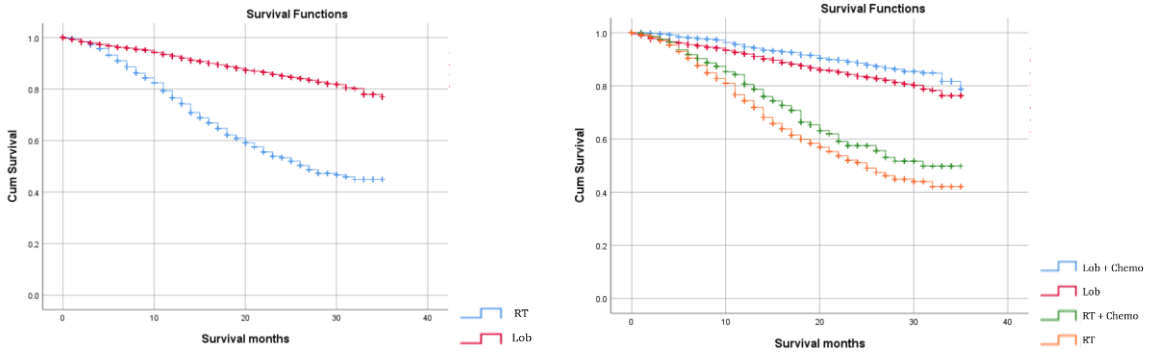
NOS	53 (1.1)	60 (5.1)	1.23 (0.78-1.93)	0.378
Others	59 (1.2)	3 (0.3)	2.29 (1.20-4.37)	0.012
Chemotherapy		0.001		
No	3550 (71.5)	786 (66.4)	1.00	
Yes	1414 (28.5)	397 (33.6)	0.82 (0.68-0.98)	0.028
Insurance		0.051		
Insured	4274 (86.1)	998 (84.4)	1.00	0.523
Medicaid	577 (11.6)	167 (14.1)	1.10 (0.86-1.41)	0.447
Uninsured	53 (1.1)	8 (0.7)	0.41 (0.10-1.65)	0.209
Unknown	60 (1.2)	10 (0.8)	0.96 (0.43-2.15)	0.919

Table 6. Unadjusted OS and CSS Stratified by Treatment – Stage IB-IIA

		Overall Survival				Cancer-Specific Survival			
Treatment	#N	Mean (SD)	95% CI	Median (SD)	95% CI	Mean (SD)	95% CI	Median (SD)	95% CI
Lobectomy	3550	30.91 (0.19)	30.54-31.27			32.14 (0.16)	31.83-32.46		
Lob + Chemo	1414	32.23 (0.25)	31.74-32.72			32.82 (0.23)	32.38-33.26		
RT	786	23.26 (0.54)	22.21-24.31	25.00 (1.76)	21.56-28.44	25.58 (0.54)	24.52-26.64		
RT + Chemo	397	25.18 (0.71)	23.79-26.57			26.84 (0.70)	25.47-28.21		

Figure 5. Unadjusted Kaplan Meier Curves OS (A) and CSS (B) Stratified by Treatment Type.

Adjusted COX Proportional Hazards (C) – Stage IB-IIA



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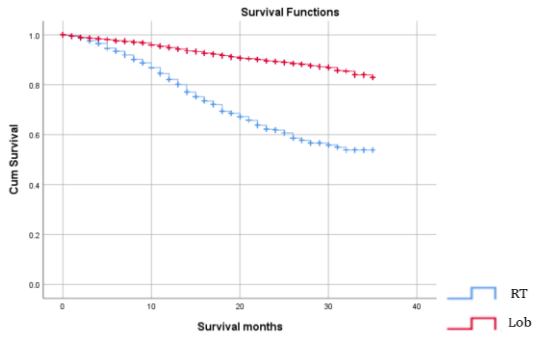

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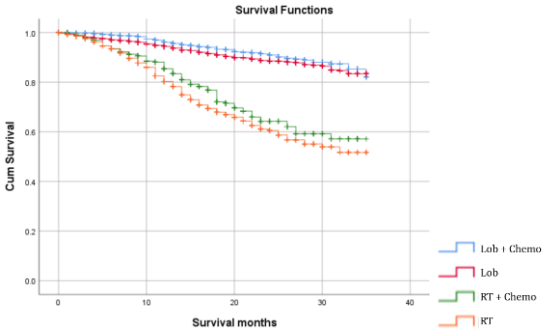

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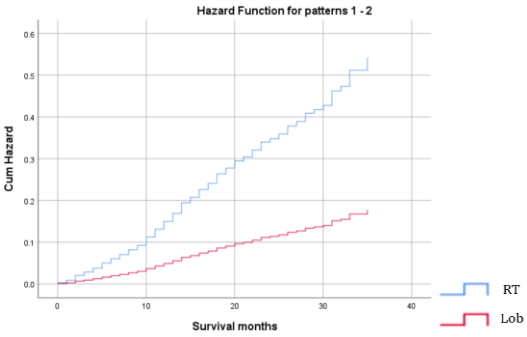
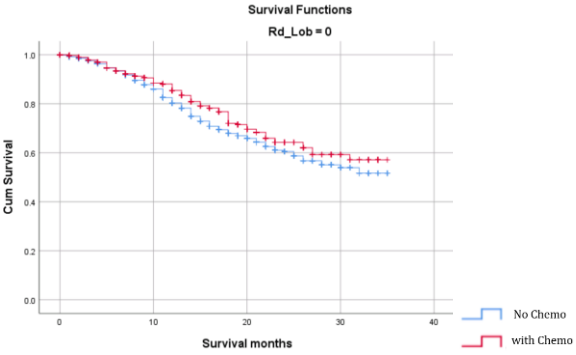


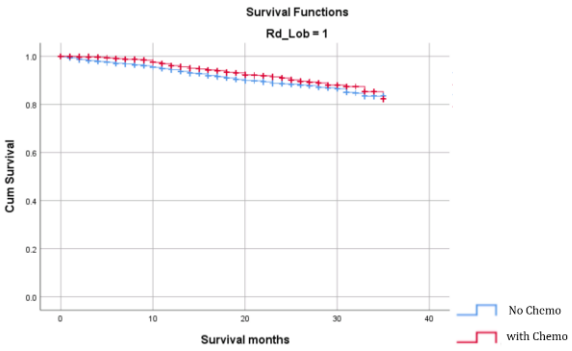
C

Fig 5. OS (A1, A2) and CSS (B1, B2) for unadjusted Lobectomy and RT cohorts, all with p < 0.001. In Adjusted COX Proportional Hazards (C), HR=3.064, P<0.001

Figure 6. Unadjusted Kaplan Meier Curves of Chemotherapy with CSS Stratified by Undergoing Lobectomy – Stage IB-IIA



A RT+/- Chemo, p = 0.01



B Lob+/-Chemo, p=0.092

Table 7. CSS of The Outcome-Related Variables – Stage IB-IIA

IB-IIA, T2N0		Cancer-specific survival			
Covariate	Mean (SD)	95% CI	Median (SD)	95% CI	#N
Age					P<0.001
<50	33.07 (0.54)	32.01-34.12			220
50-59	32.72 (0.30)	32.14-32.30			885
60-69	31.99 (0.22)	31.56-32.42			1981
70-79	30.84 (0.24)	30.36-31.32			2179
>=80	28.00 (0.47)	27.08-28.91			882
Sex					P<0.001
Male	31.69 (0.19)	31.33-32.06			3064
Female	30.61 (0.21)	30.21-31.02			3083
Grade					P<0.001
I	32.90 (0.28)	32.35-33.45			875
II	31.82 (0.19)	31.44-32.19			2869
III	29.68 (0.26)	29.17-30.19			2298
Undifferentiated	31.26 (1.06)	29.20-33.32			105
Histology					P<0.001
Adenocarcinoma	32.08 (0.16)	31.77-32.39			3853
Squamous	29.77 (0.27)	29.23-30.30			2041
Carcinoid	26.76 (1.37)	24.06-29.45			78
NOS	27.65 (1.20)	25.30-30.00			113
Others	29.02 (1.68)	25.72-32.32			62
Chemotherapy					P=0.095
No	31.03 (0.17)	30.68-31.34			4336
Yes	31.40 (0.25)	31.02-31.98			1811

Mean (SD) follow-up of OS for patients was 30.91 (0.19) months in the Lobectomy group and 23.26 (0.54) months in the RT group in stage IB-IIA. The estimated CSS in surgery group alone vs. RT alone were [32.14 (0.16), 95% CI 31.83-32.46] and 25.58 (0.54) [95% CI 24.52-26.64]. There was a statistically significant difference in CSS between the two strategies (log-rank $p < 0.001$; HR = 3.06). The difference in CSS between with/out chemotherapy in RT group was significant ($p < 0.001$). OS and CSS were both improved when lobectomy combined with the Chemotherapy, as well as in RT group. The outcome-related multivariable lead to significant difference in CSS in Table 7.

3. Stage IIB

Table 8. Descriptive Statistics Comparing Patients Undergoing Surgery vs. RT with Adjusted COX Proportional Hazards - Stage IIB, T1-2N1

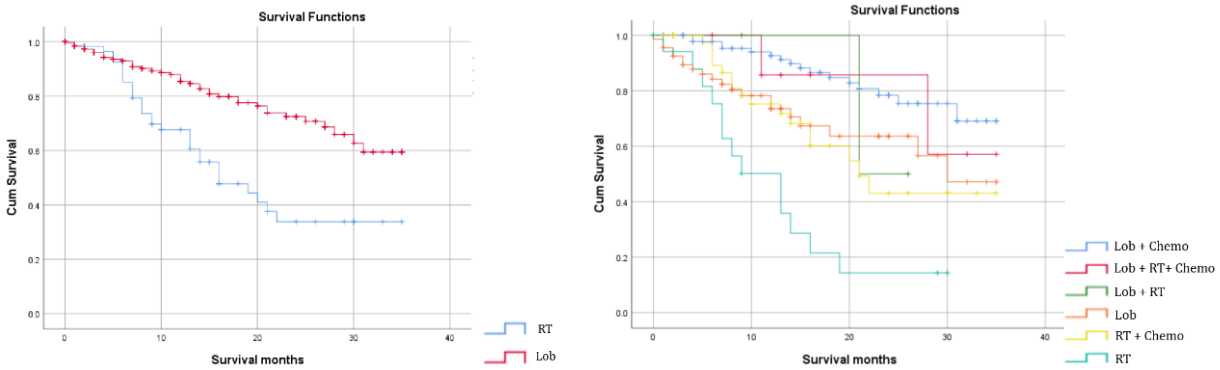
T1-2, N1 Covariate	Lobectomy N (%)	RT N (%)	p	HR (95% CI)	P
	186	61			
Age			0.075		
<50	7 (3.8)	1 (1.6)		1.00	0.400
50-59	32 (17.2)	5 (8.2)		976.81 (0.00-4.33E)	0.904
60-69	66 (35.5)	16 (26.2)		1801.84 (0.00-7.96E)	0.896
70-79	64 (34.4)	40 (49.2)		2826.97 (0.00-1.23E)	0.889
>=80	17 (9.1)	9 (14.8)		2121.28 (0.00-9.39E)	0.893
Race			0.006		
White	159 (85.5)	49 (80.3)		1.00	0.904
Black	12 (6.5)	11 (18.0)		1.00 (0.39-2.59)	0.994
Others	15 (8.1)	1 (1.6)		1.34 (0.38-4.72)	0.653
Sex			1.00		
Male	107 (57.5)	35 (57.4)		1.58 (0.85-2.94)	0.145
Female	79 (42.5)	26 (42.6)		1.00	
Grade			0.527		
I	13 (7.0)	4 (6.6)		1.00	0.083
II	94 (38.1)	20 (32.8)		2.27 (0.29-17.96)	0.438
III	133 (53.8)	37 (60.7)		5.09 (0.68-38.40)	0.115
Undifferentiated	3 (1.2)	0 (0.0)		0.001 ((0.00-4.81E)	0.915
Histology			0.004		
Adenocarcinoma	94 (50.5)	14 (23.0)		1.00	0.247
Squamous	80 (43.0)	42 (68.9)		1.29 (0.67-2.47)	0.442
Carcinoid	4 (2.2)	1 (1.6)		0.92 (0.22-3.76)	0.904
NOS	6 (3.2)	4 (6.6)		2.02 (0.52-7.86)	0.309
Others	2 (1.1)	0 (0.0)		11.92 (1.23-116.01)	0.033
Chemotherapy			0.222		
No	72 (38.7)	18 (29.5)		1.00	
Yes	114 (61.3)	43 (70.5)		0.41 (0.22-0.77)	0.005
Insurance	v		0.635		
Insured	162 *87.1)	49 (80.3)		1.00	0.791
Medicaid	17 (9.1)	9 (14.8)		0.80 (0.32-1.99)	0.630
Uninsured	4 (2.2)	2 (3.3)		1.58 (0.34-7.42)	0.565
Unknown	3 (1.6)	1 (1.6)		1.82 (0.23-14.30)	0.571

Table 9. Unadjusted OS and CSS stratified by treatment – Stage IIB, T1-2N1

T1-2, N1	IIB	Overall Survival				Cancer-Specific Survival			
Treatment	#N	Mean (SD)	95% CI	Median (SD)	95% CI	Mean (SD)	95% CI	Median (SD)	95% CI
Lob+ Chemo	106	30.02 (1.10)	27.86-32.17			30.88 (1.04)	28.84-32.91		
Lob +RT+Chemo	8	29.57 (3.30)	23.11-36.04			29.57 (3.30)	23.11-36.04		
Lob+RT	3	23.50 (1.77)	20.04-26.97	21.00		23.50 (1.77)	20.04-26.97	21.00	
Lobectomy	69	24.29 (1.89)	20.59-28.00	30.00		27.31 (1.80)	23.79-30.83		
RT + Chemo	43	22.71 (2.18)	18.43-26.98	21.00 (3.54)	14.06 - 27.94	23.51 (2.20)	19.19-27.82	21.00	
RT	18	12.63 (2.18)	8.36-16.89	13.00 (3.00)	7.11-18.88	13.98 (2.41)	9.25-18.71	13.00 (4.60)	3.98-20.01

Figure 7. Unadjusted Kaplan Meier Curves OS (A) and CSS (B) Stratified by Treatment Type.

Adjusted COX Proportional Hazards (C) – Stage IIB, T1-2N1



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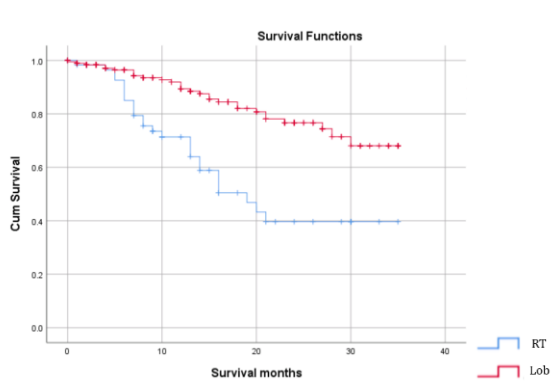

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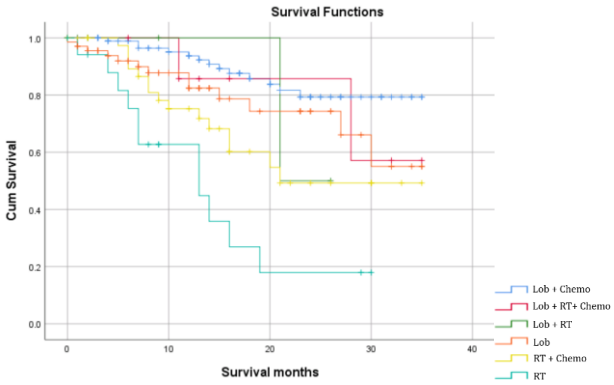

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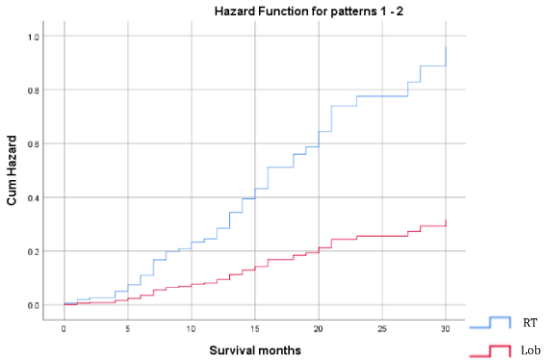


C

Fig 7. OS (A1, A2) and CSS (B1, B2) for unadjusted Lobectomy and RT cohorts, all with $p < 0.001$. In Adjusted COX Proportional Hazards (C), HR=3.03, $p < 0.001$.

Table 10. CSS of The Outcome-Related Variables– Stage IIB, T1-2N1

T1-2, N1			Cancer-specific survival		
Covariate	Mean (SD)	95% CI	Median (SD)	95% CI	#N
Chemotherapy					P=0.014
No	24.19 (1.66)	20.93-27.44	30.00		90
Yes	28.57 (1.00)	26.59-30.54			157
Grade (censored)					

Table 11. Descriptive Statistics Comparing Patients Undergoing Surgery vs. RT with Adjusted COX Proportional Hazards - Stage IIB, T3N0

T3N0	Lobectomy	RT	p	HR (95% CI)	P
Covariate	N (%)	N (%)			
	1174	522			
Age			<0.001		
<50	40 (3.4)	7 (1.3)		1.00	0.042
50-59	192 (16.4)	47 (9.0)		1.46 (0.51-4.19)	0.480
60-69	421 (35.9)	149 (28.5)		1.80 (0.65-4.95)	0.258
70-79	424 (36.1)	182 (34.9)		2.45 (0.89-6.75)	0.084
>=80	97 (8.3)	137 (26.2)		2.18 (0.77-6.20)	0.143
Race			0.009		
White	990 (84.0)	424 (81.5)		1.00	0.296
Black	105 (9.0)	72 (13.8)		1.16 (0.82-1.65)	0.411
Others	69 (5.9)	24 (4.6)		1.40 (0.88-2.22)	0.158
Sex			0.018		
Male	615 (52.4)	306 (58.6)		1.16 (0.91-1.58)	0.218
Female	559 (47.6)	216 (41.4)		1.00	
Grade			<0.001		
I	197 (16.8)	43 (8.2)		1.00	0.002
II	466 (39.7)	172(33.0)		1.78 (1.06-2.97)	0.029
III	478 (40.7)	292 (55.9)		2.40 (1.55-3.99)	0.001
Undifferentiated	33 (2.8)	15 (2.9)		3.32 (1.59-7.42)	0.003
Histology			<0.001		
Adenocarcinoma	757 (64.5)	173 (33.1)		1.00	0.032
Squamous	362 (30.8)	298 (57.1)		1.34 (1.03-1.74)	0.030
Carcinoid	19 (1.6)	6 (1.1)		2.77 (1.35-5.68)	0.006
NOS	17 (1.4)	37 (7.1)		1.33 (0.75-2.35)	0.326
Others	19 (1.6)	8 (1.5)		1.61 (0.76-3.39)	0.210
Chemotherapy			0.01		
No	625 (53.2)	242 (46.4)		1.00	
Yes	549 (46.8)	280 (53.6)		0.73 (0.57-0.95)	0.013
Insurance			0.335		
Insured	1024 (87.2)	438 (83.9)		1.00	0.883
Medicaid	130 (11.1)	74 (14.2)		1.00 (0.70-1.43)	0.997
Uninsured	12 (1.0)	6 (1.1)		0.96 (0.30-3.04)	0.943
Unknown	8 (0.7)	4 (0.8)		0.44 (0.06-3.20)	0.420

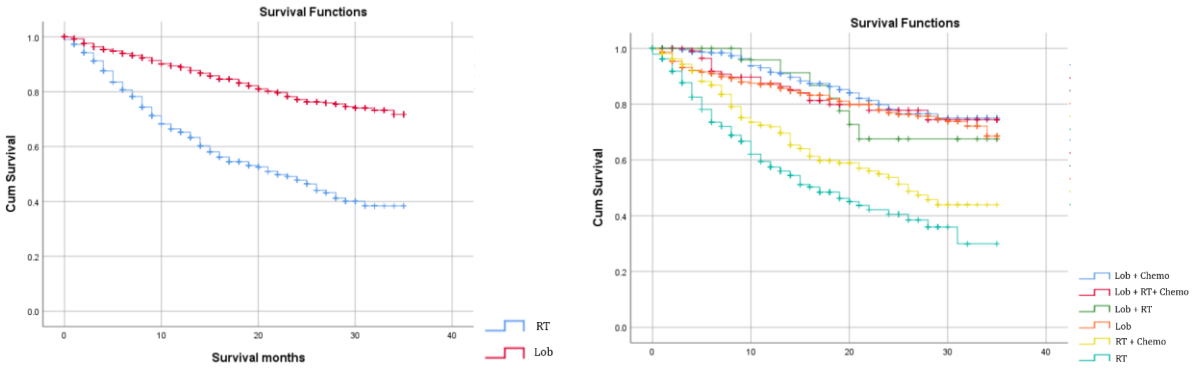
Table 12. Unadjusted OS and CSS Stratified by Treatment – Stage IIB, T3N0

T3N0	IIB	Overall Survival				Cancer-Specific Survival			
Treatment	#N	Mean (SD)	95% CI	Median (SD)	95% CI	Mean (SD)	95% CI	Median (SD)	95% CI

Lob+ Chemo	424	30.42 (0.57)	29.30-31.55			30.83 (0.56)	29.74-31.92		
Lob +RT+Chemo	125	29.47 (1.07)	27.37-31.58			30.42 (1.00)	28.45-32.39		
Lob+RT	31	29.09 (1.89)	25.39-32.78			29.96 (1.76)	26.52-33.40		
Lobectomy	594	29.07 (0.53)	28.04-31.11			30.92 (0.47)	30.01-31.83		
RT + Chemo	280	22.87 (0.92)	21.07-24.68	26.00 (2.51)	21.08-30.92	24.22 (0.92)	22.41-26.03		
RT	242	19.08 (1.04)	17.04-21.22	17.00 (2.56)	11.98-22.02	21.74 (1.11)	19.57-23.91	26.00 (4.25)	17.67-34.33

Figure 8. Unadjusted Kaplan Meier Curves OS (A) and CSS (B) Stratified by Treatment Type.

Adjusted COX Proportional Hazards (C) – Stage IIB, T3N0



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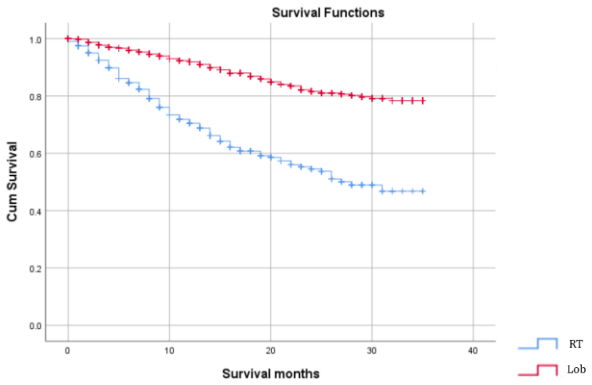

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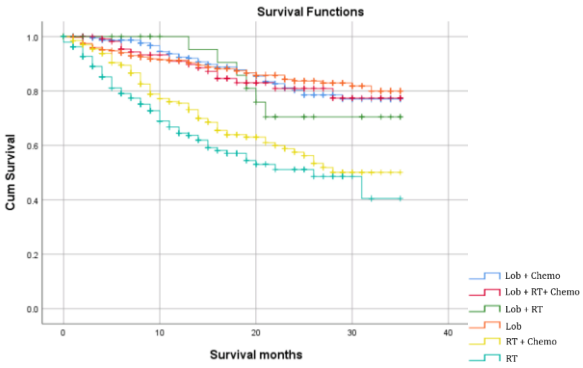

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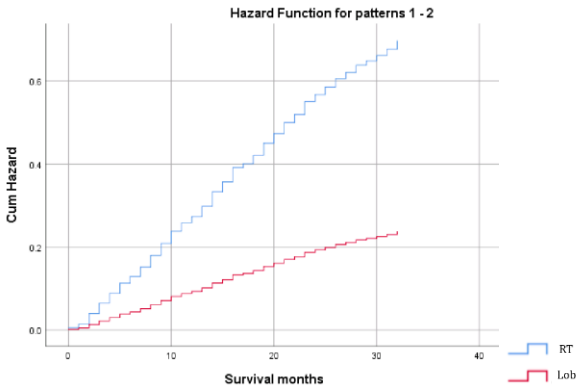


C

Fig 8. OS (A1, A2) and CSS (B1, B2) for unadjusted Lobectomy and RT cohorts, with all p < 0.001. In Adjusted COX Proportional Hazards (C), HR=2.94, p < 0.001.

Table 13. CSS of The Outcome-Related Variables – Stage IIB, T3N0

T3N0		Cancer-specific survival			
Covariate	Mean (SD)	95% CI	Median (SD)	95% CI	#N
Age					p<0.001
<50	31.10 (1.35)	28.46-33.74			47
50-59	30.23 (0.78)	28.70-31.77			239
60-69	29.37 (0.53)	28.33-30.40			570
70-79	27.48 (0.58)	26.34-28.62			606
>=80	26.36 (1.01)	24.37-28.35			234

Grade					p<0.001
I	32.17 (0.63)	30.94-33.41			240
II	29.28 (0.51)	28.27-30.29			638
III	26.93 (0.51)	25.92027.95			770
Undifferentiated	22.36 (2.20)	18.95-26.68			48
Histology					P<0.001
Adenocarcinoma	30.48 (0.38)	29.72-31.23			930
Squamous	26.44 (0.58)	25.30-27.58			660
Carcinoid	20.53 (2.78)	15.09-25.96	26.00 (9.72)	6.95-45.05	25
NOS	23.98 (2.23)	19.60-28.36	27.00		54
Others	20.94 (2.56)	15.95-25.98	21.00		27
Chemotherapy					p=0.578
No	28.41 (0.47)	27.50-29.33			867
Yes	28.56 (0.46)	27.64-29.46			829

The clinical TNM staging was separated into two groups, T1-2N1 and T3N0, Undergoing the Lobectomy with Chemotherapy, Lobectomy with Chemotherapy plus Radiation treatment, Lobectomy alone, Radiation with Chemotherapy, and Radiation treatment alone.

Mean (SD) follow-up of CSS in the Lobectomy with chemotherapy group was 30.88 (1.04) month and 29.57 (3.30) months in the triple combo group with T1-2N1, 30.83 (0.56) and 30.42 (1.00) month with T3N0, respectively. With T1-2N1, pooled estimated median follow-up of CSS in RT combined with chemotherapy group were 21 and 13 months in RT alone. The HR of RT compared to lobectomy resection indicated a significant difference with both T1-2N1 and T3N0 groups.

4. Stage IIIA

Table 14. Descriptive Statistics Comparing Patients Undergoing Lobectomy vs. RT with Adjusted COX Proportional Hazards - Stage IIIA, T3N1 & T4N0-1

IIIA, N<=1 Covariate	Lobectomy N (%)	RT N (%)	p	HR (95% CI)	P
	556	761			
Age			0.001		
<50	18 (3.2)	23 (3.0)		1.00	0.657
50-59	110 (19.8)	115 (15.1)		1.10 (0.55-2.22)	0.789
60-69	173 (30.9)	278 (36.5)		1.02 (0.51-2.02)	0.956
70-79	208 (37.4)	241 (31.7)		1.26 (0.63-2.51)	0.509
>=80	48 (8.6)	104 (13.7)		1.16 (0.56-2.41)	0.606
Race			0.13		
White	445 (80.3)	609 (80.3)		1.00	0.538
Black	62 (11.2)	103 (13.6)		0.88 (0.64-1.22)	0.445
Others	47 (8.5)	46 (6.1)		0.83 (0.55-1.25)	0.374
Sex			0.024		
Male	297 (53.4)	454 (59.7)		1.26 (1.03-1.55)	0.029
Female	259 (46.6)	307 (40.3)		1.00	
Grade			<0.001		
I	73 (13.1)	48 (6.3)		1.00	0.003
II	199 (35.8)	261 (34.3)		0.95 (0.62-1.46)	0.811
III	273 (49.1)	438 (57.6)		1.45 (0.95-2.19)	0.082
Undifferentiated	11 (2.0)	14 (1.8)		1.31 (0.57-3.01)	0.523
Histology			<0.001		
Adenocarcinoma	342 (61.5)	259 (34.0)		1.00	0.045
Squamous	172 (30.9)	429 (56.4)		1.37 (1.09-1.72)	0.007
Carcinoid	11 (2.0)	12 (1.6)		0.70 (0.28-1.76)	0.451
NOS	15 (2.7)	52 (6.8)		1.27 (0.80-2.00)	0.314
Others	16 (2.9)	9 (1.2)		1.65 (0.79-3.41)	0.180
Chemotherapy			<0.001		
No	208 (37.4)	197 (25.9)		1.00	
Yes	348 (62.6)	564 (74.1)		0.66 (0.52-0.83)	<0.001
Insurance			0.011		
Insured	472 (84.9)	601 (79.0)		1.00	0.103
Medicaid	70 (12.6)	132 (17.3)		1.36 (1.03-1.80)	0.031
Uninsured	7 (1.3)	22 (2.9)		0.75 (0.35-1.62)	0.459
Unknown	7 (1.3)	6 (0.8)		1.55 (0.57-4.22)	0.393

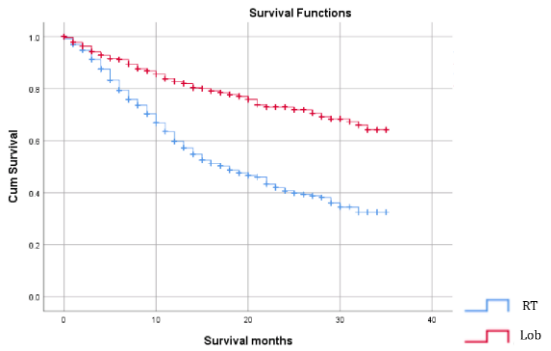
Table 15. Unadjusted OS and CSS Stratified by Treatment – Stage IIIA, T3N0 & T4N0-1

IIIA, N<=1		Overall Survival				Cancer-Specific Survival			
Treatment	#N	Mean	95% CI	Median	95% CI	Mean	95% CI	Median	95% CI

		(SD)				(SD)				
Lob+ Chemo	242	29.31 (0.77)	27.81-30.81			29.92 (0.76)	28.14-31.10			
Lob +RT+Chemo	106	28.33 (1.18)	26.02-30.63			28.86 (1.15)	26.61-31.10			
Lob+RT	13	29.28 (3.05)	23.30-35.25			29.28 (3.05)	23.30-35.25			
Lobectomy	195	25.57 (0.64)	23.49-27.68			27.37 (1.02)	25.37-29.37			
RT + Chemo	564	20.57 (0.64)	19.32-21.82	19.00 (2.02)	15.04-22.96	21.71 (0.65)	20.43-22.99	23.00 (2.54)	18.02-27.96	
RT	197	17.29 (1.05)	15.23-19.35	15.00 (2.00)	11.18-18.83	18.58 (1.10)	16.42-20.74	18.00 (3.31)	11.52-24.48	

Figure 9. Unadjusted Kaplan Meier curves OS (A) and CSS (B) Stratified by Treatment Type.

Adjusted COX Proportional Hazards (C) – Stage IIIA, T3N1 & T4N0-1



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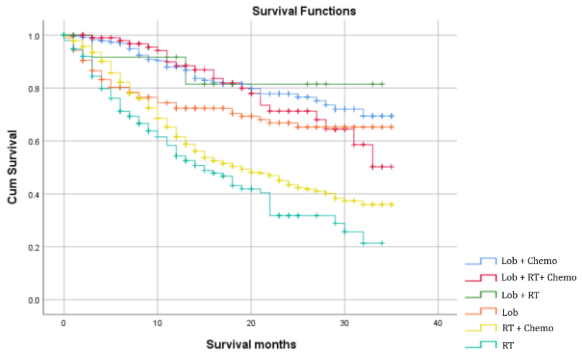

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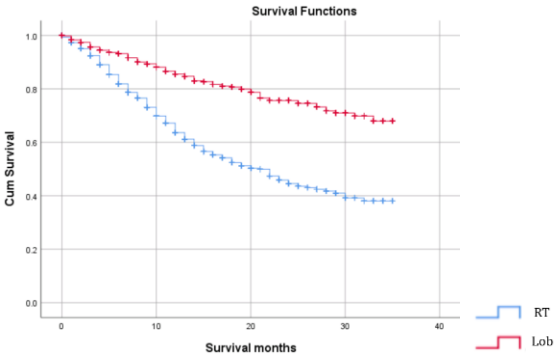

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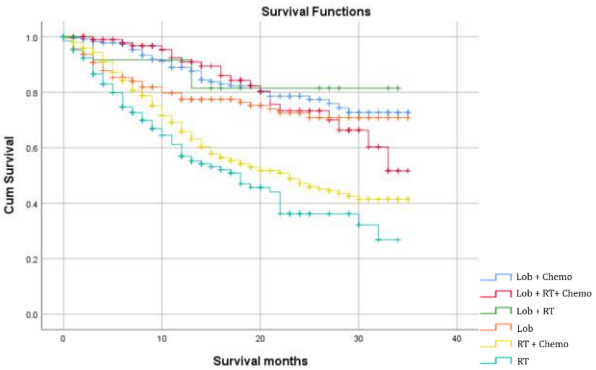

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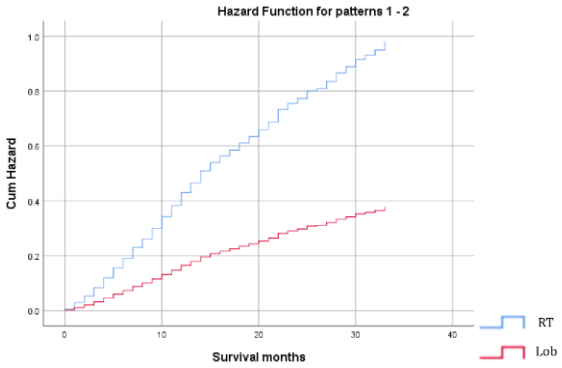


C

Fig 9. OS (A1, A2) and CSS (B1, B2) for unadjusted Lobectomy and RT cohorts, all with $p < 0.001$. In Adjusted COX Proportional Hazards (C), HR=2.60, $p < 0.001$.

Table 16. CSS of The Outcome-Related Variables– Stage IIIA, T3N1 & T4N0-1

	Cancer-specific survival				
IIIA, N<=1					
Covariate	Mean (SD)	95% CI	Median (SD)	95% CI	#N
Sex					p=0.011
Male	23.49 (0.56)	22.39-24.58	33.00		751
Female	25.59 (0.61)	24.39-26.79			566
Grade					p<0.001
I	27.47 (1.23)	25.06-29.88			121
II	26.05 (0.68)	24.72-27.37			460
III	22.72 (0.58)	21.58-23.85	27.00 (2.56)	21.98-32.03	711
Undifferentiated	25.64 (2.71)	20.34-30.95			25
Histology					p<0.001
Adenocarcinoma	26.89 (0.57)	25.78-28.01			601
Squamous	21.98 (0.64)	20.73-23.22	23.00 (2.88)	17.35-28.65	601
Carcinoid	25.72 (2.25)	21.31-30.14	29.00 (10.83)	7.77-50.22	23
NOS	22.10 (1.91)	18.35-25.85	25.00 (4.09)	16.98-33.02	67
Others	22.67 (3.13)	16.53-28.81			25
Chemotherapy					p=0.095
No	23.57 (0.79)	22.02-25.11			405
Yes	24.74 (0.49)	23.78-25.69			912

Table 17. Descriptive Statistics Comparing Patients Undergoing Surgery vs. RT with Adjusted COX Proportional Hazards - Stage IIIA, T2N2

IIIA, N=2 Covariate	Lobectomy N (%)	RT N (%)	p	HR (95% CI)	P
Age			<0.001		
<50	77 (5.7)	58 (3.1)		1.00	0.003
50-59	272 (20)	337 (17.9)		0.98 (0.66-1.45)	0.905
60-69	498 (36.6)	626 (33.2)		1.18 (0.81-1.72)	0.399
70-79	412 (30.3)	596 (31.6)		1.31 (0.89-1.91)	0.166
>=80	102 (7.5)	269 (14.3)		1.56 (1.04-2.33)	0.033
Race			<0.001		
White	1099 (81.0)	1501 (79.8)		1.00	0.226
Black	129 (9.5)	258 (13.7)		0.84 (0.68-1.03)	0.085
Others	128 (9.4)	121 (6.4)		0.96 (0.75-1.24)	0.772
Sex			<0.001		
Male	622 (45.7)	1074 (56.9)		1.24 (1.09-1.42)	0.001
Female	739 (54.3)	812 (43.1)		1.00	
Grade			<0.001		
I	99 (7.3)	93 (4.9)		1.00	0.001
II	620 (45.6)	599 (31.8)		1.48 (1.05-2.09)	0.026
III	627 (46.1)	1145 (60.7)		1.78 (1.27-2.50)	0.001
Undifferentiated	15 (1.1)	49 (2.6)		1.64 (0.97-2.77)	0.062
Histology			<0.001		
Adenocarcinoma	993 (73.0)	751 (39.8)		1.00	<0.001
Squamous	313 (23.0)	958 (50.8)		1.35 (1.17-1.56)	<0.001
Carcinoid	20 (1.5)	32 (1.7)		1.65 (1.07-2.55)	0.024
NOS	25 (1.8)	138 (7.3)		1.64 (1.27-2.12)	<0.001
Others	10 (0.7)	7 (0.4)		1.83 (0.91-3.71)	0.092
Chemotherapy			<0.001		
No	299 (22.0)	312 (16.5)		1.00	
Yes	1062 (78.0)	1574 (83.5)		0.50 (0.43-0.59)	<0.001
Insurance			<0.001		
Insured	1182 (86.8)	1523 (80.8)		1.00	0.254
Medicaid	153 (11.2)	303 (16.1)		1.15 (0.95-1.39)	0.146
Uninsured	13 (1.0)	40 (2.1)		0.99 (0.58-1.39)	0.968
Unknown	13 (1.0)	20 (1.1)		1.51 (0.87-2.60)	0.148

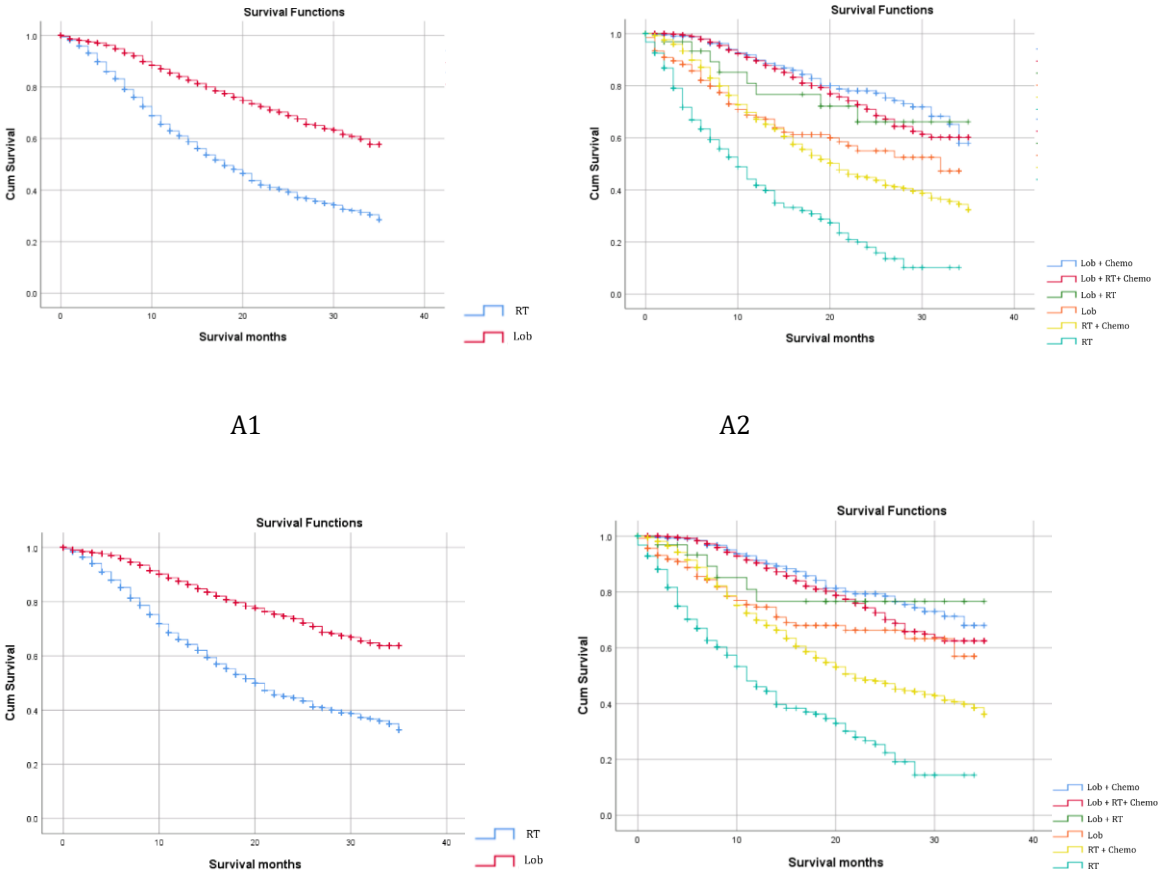
Table 18. Unadjusted OS and CSS stratified by treatment – Stage IIIA, T2N2

IIIA, N=2	IIB	Overall Survival				Cancer-Specific Survival			
Treatment	#N	Mean (SD)	95% CI	Median (SD)	95% CI	Mean (SD)	95% CI	Median (SD)	95% CI
Lob+ Chemo	451	29.37 (0.60)	28.31-30.64			29.97 (0.58)	28.83-31.12		

Lob +RT+Chemo	611	28.37 (0.52)	27.36-29.38			28.76 (0.51)	27.76-29.76		
Lob+RT	32	27.22 (2.33)	22.65-31.79			28.66 (2.29)	24.18-33.14		
Lobectomy	267	22.57 (1.02)	20.57-24.57	32.00		24.99 (1.00)	23.04-26.94		
SBRT + Chemo	1574	21.42 (0.37)	20.69-22.15	21.00 (1.05)	18.95-23.05	22.37 (0.38)	21.63-23.11	22.00 (1.29)	19.46-24.54
SBRT	312	13.07 (0.70)	11.68-14.45	10.10 (0.81)	8.41-11.59	14.58 (0.80)	13.02-16.14	11.00 (1.02)	9.01-12.99

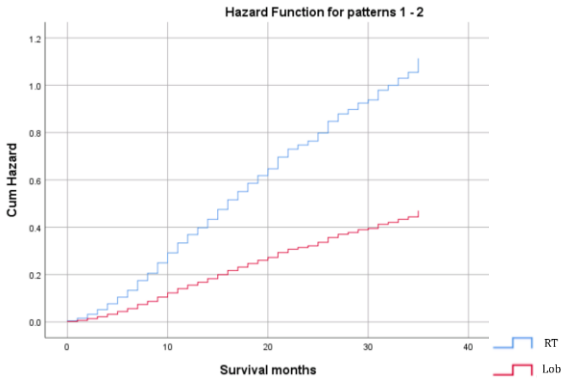
Figure 10. Unadjusted Kaplan Meier Curves OS (A) and CSS (B) Stratified by Treatment Type.

Adjusted COX Proportional Hazards (C) – Stage IIIA, T2N2



A1 A2

B1 B2



C

Fig 10. OS (A1, A2) and CSS (B1, B2) for unadjusted Lobectomy and RT cohorts, all with p < 0.001. In Adjusted COX Proportional Hazards (C), HR=2.38, p < 0.001.

Table 19. CSS of The Outcome-Related Variables– Stage IIIA, T2N2

IIIA, N=2			Cancer-specific survival		
Covariate	Mean (SD)	95% CI	Median (SD)	95% CI	#N
Age					p<0.001
<50	27.39 (1.15)	25.14-29.63	33.00		135
50-59	26.14 (0.59)	24.98027.30			609
60-69	24.83 (0.45)	23.96-25.71	33.00 (2.11)	28.87-37.13	1124
70-79	23.35 (0.48)	22.41-24.30	27.00 (2.37)	22.36-31.64	1008
>=80	19.70 (0.82)	18.09-21.31	18.00 (1.58)	14.90-21.10	371
Sex					p<0.001
Male	22.85 (0.37)	22.12-23.58	26.00 (1.42)	23.21-28.79	1696
Female	25.65 (0.38)	24.91-26.39			1551
Grade					p<0.001
I	27.58 (0.90)	25.82-29.34			192
II	25.46 (0.42)	24.63-26.29	35.00 (4.77)	25.66-44.34	1219
III	22.92 (0.37)	22.20-23.64	26.99 (1.63)	22.81-29.19	1772
Undifferentiated	20.40 (1.69)	17.09-23.71	18.00 (3.98)	10.20-25.80	64
Histology					p<0.001
Adenocarcinoma	26.75 (0.35)	26.07-27.42			1744
Squamous	21.64 (0.43)	20.79-22.49	21.00 (1.32)	18.41-23.59	1271
Carcinoid	19.34 (1.68)	16.06-22.63	19.00 (2.41)	14.27-23.93	52
NOS	18.63 (1.10)	16.48-20.79	17.00 (2.68)	11.75-22.25	163
Others	20.23 (3.31)	13.75-26.71	31.00 (12.52)	6.47-55.53	17
Chemotherapy					p<0.001
No	19.88 (0.69)	18.52-21.24	20.00 (2.12)	15.85-24.15	611
Yes	25.08 (0.29)	24.52-25.64	33.00		2636

The clinical TNM staging was separated into two groups, N<=1 and N=2, undergoing the Lobectomy, Chemotherapy, and Radiation treatment into variate combo treatment in the table. Mean (SD) follow-up of CSS in the Lobectomy with chemotherapy group was 29.92 (0.76) month and 28.86 (1.15) months in the CRT combo group with T3N1 & T4N0-1, 29.97 (0.58) and 28.76 (0.51) month with T2N2, respectively. With N <= 1, pooled estimated median follow-up of CSS in RT combined with chemotherapy were 22 and 11 months in RT alone, 20 vs. 8 months with N2, respectively. The HR of RT compared to lobectomy resection (2.60 with N <= 1; 2.38 with N = 2) indicated a significant difference with both Stage IIIA groups.

5. Stage IIIB-IIIC

Table 20. Descriptive Statistics Comparing Patients Undergoing Surgery vs. RT with Adjusted COX Proportional Hazards - Stage IIIB & IIIC

IIIB & IIIC Covariate	Lobectomy N (%)	RT N (%)	p	HR (95% CI)	P
	115	1467			
Age			0.902		
<50	5 (4.3)	68 (4.6)		1.00	0.458
50-59	28 (24.3)	320 (21.8)		0.83 (0.58-1.19)	0.321
60-69	42 (36.5)	502 (34.2)		0.76 (0.53-1.08)	0.123
70-79	30 (26.1)	429 (29.2)		0.79 (0.55-1.13)	0.199
>=80	10 (8.7)	148 (10.1)		0.69 (0.45-1.05)	0.083
Race			0.115		
White	80 (69.6)	1103 (75.2)		1.00	0.386
Black	19 (16.5)	242 (16.5)		1.07 (0.87-1.32)	0.513
Others	16 (13.9)	122 (8.3)		0.85 (0.63-1.14)	0.268
Sex			0.138		
Male	61 (53.0)	886 (60.4)		1.08 (0.92-1.26)	0.355
Female	54 (47.0)	581 (39.6)		1.00	
Grade			0.009		
I	8 (7.0)	57 (3.9)		1.00	0.176
II	48 (41.7)	430 (29.3)		1.04 (0.70-1.54)	0.850
III	57 (49.6)	941 (64.1)		1.12 (0.77-1.64)	0.552
Undifferentiated	2 (1.7)	39 (2.7)		1.74 (0.98-3.08)	0.060

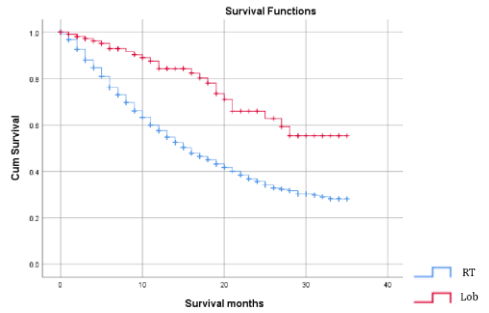
Histology			<0.001		
Adenocarcinoma	80 (69.6)	566 (38.6)		1.00	<0.001
Squamous	28 (24.3)	746 (50.9)		1.37 (1.16-1.63)	<0.001
Carcinoid	3 (2.6)	26 (1.8)		1.49 (0.86-2.59)	0.158
NOS	2 (1.7)	121 (8.2)		1.65 (1.24-2.20)	0.001
Others	2 (1.7)	8 (0.5)		1.34 (0.49-3.62)	0.570
Chemotherapy			0.023		
No	26 (22.6)	214 (14.6)		1.00	
Yes	89 (77.4)	1253 (85.4)		0.36 (0.29-0.44)	<0.001
Insurance			0.225		
Insured	97 (84.3)	1152 (78.5)		1.00	0.282
Medicaid	17 (14.8)	250 (17.0)		0.96 (0.78-1.19)	0.700
Uninsured	1 (0.9)	41 (2.8)		1.46 (0.97-2.21)	0.072
Unknown	0 (0.0)	24 (1.6)		1.17 (0.62-2.20)	0.631

Table 21. Unadjusted OS and CSS Stratified by Treatment – Stage IIIB & IIIC

IIIB & IIIC		Overall Survival				Cancer-Specific Survival			
Treatment	#N	Mean (SD)	95% CI	Median (SD)	95% CI	Mean (SD)	95% CI	Median (SD)	95% CI
Lob+ Chemo	36	30.69 (1.91)	26.95 - 34.33			30.69 (1.91)			
Lob +RT+Chemo	53	26.12 (1.68)	22.82 - 29.42			26.57 (1.66)	23.33-29.82		
Lob+RT	2	20.00 (0.00)	20.00 - 20.00	20.00		20.00 (0.00)	20.00-20.00	20.00	
Lobectomy	24	14.41 (1.82)	10.85 - 17.97	18.00 (8.79)	0.76-35.24	14.41 (1.82)	10.85-17.97	18.00 (8.79)	0.76-35.24
RT + Chemo	1253	20.00 (0.43)	19.17 - 20.84	19.00 (0.96)	17.12 - 20.88	20.66 (0.43)	19.81-21.51	20.00 (1.05)	17.95 - 22.05
RT	214	10.05 (0.73)	8.62-11.48	7.00 (0.92)	5.20-8.80	11.38 (0.84)	9.73-13.03	8.00 (0.92)	6.20-9.81

Figure 11. Unadjusted Kaplan Meier curves OS (A) and CSS (B) Stratified by Treatment Type.

Adjusted COX Proportional Hazards (C) – Stage IIIB & IIIC



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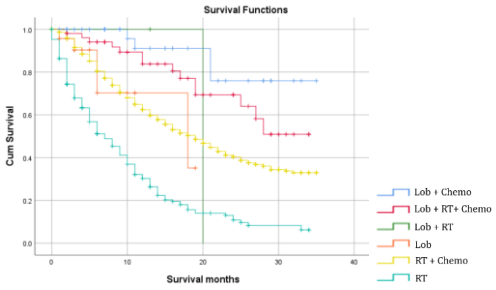

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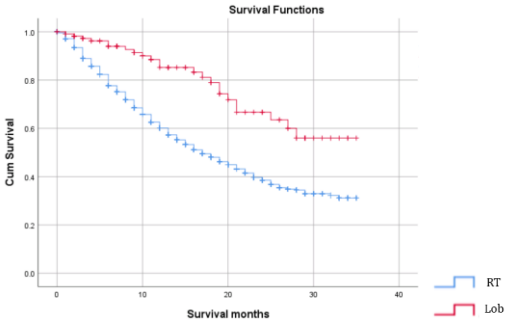

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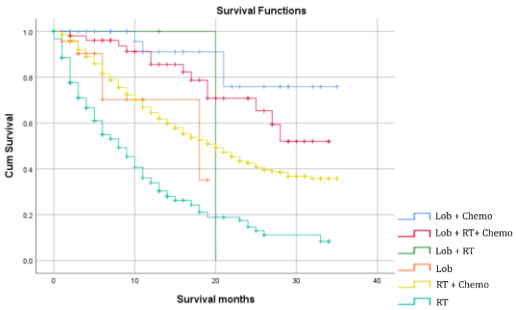

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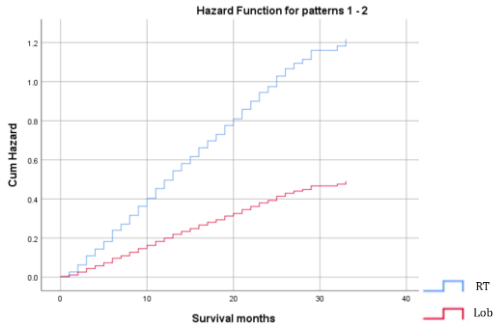

C

Fig 11. OS (A1, A2) and CSS (B1, B2) for unadjusted Lobectomy and RT cohorts, all with $p < 0.001$. In Adjusted COX Proportional Hazards (C), HR=2.49, $p < 0.001$.

Table 22. CSS of The Outcome-Related Variables – Stage IIIB & IIIC

	Cancer-specific survival				
IIIB & IIIC Covariate	Mean (SD)	95% CI	Median (SD)	95% CI	#N

Histology					p<0.001
Adenocarcinoma	22.02 (0.59)	21.04-23.36	24.00 (1.34)	21.38-26.62	646
Squamous	18.31 (0.56)	17.21-19.40	15.00 (0.99)	13.06-16.94	774
Carcinoid	15.32 (2.07)	11.27-19.37	15.00 (4.50)	6.19-23.81	29
NOS	17.23 (1.41)	14.48-19.99	13.00 (2.28)	8.53-17.47	123
Others	16.95 (0.39)	12.97-20.94	20.00 (4.68)	10.83-29.17	10
Chemotherapy					p<0.001
No	11.91 (0.83)	10.29-13.54	9.00 (0.93)	7.18-10.82	240
Yes	21.18 (0.42)	20.36-22.00	21.00 (1.12)	18.81-23.19	1342

The clinic TNM staging IIIB and IIIC grouped into one, undergoing the surgical resection of lobectomy and Radiation treatment. Mean (SD) of CSS in the Lobectomy with chemotherapy group was 30.69 (1.91) month compared to 20.66 (0.43) months in CRT group. The HR of RT compared to lobectomy resection suggested significant difference, with HR=2.49, $p < 0.001$.

IV. DISCUSSION

Curative resection with lobectomy is an option for patients with NSCLC only when early stage disease is present. Given the moderate sensitivity of NSCLC to chemotherapy, approximately 80% of NSCLC patients are candidates for chemotherapy at some point during the whole disease course to deliver a better health outcome or prevent relapse. [21] When patients are not operable candidates because either multiple nodal stations are involved (N2-N3), or the primary tumor is unresectable or would require a comorbid pneumonectomy (T4), the only potentially curative option is with radiation. Currently, chemotherapy given concurrently with radiation therapy is the standard of care for NSCLC patients with a locally advanced stage IIIB-C disease. Many previous studies suggested that the combination of chemotherapy with radiation therapy improves OS and disease-free survival. Chemoradiation (CRT), followed by surgery, might possibly benefit survival and may downstage patients who were initially not candidates for surgery. However, CRT followed by surgery has been compared to definitive CRT alone, and there was no difference in OS. [22]

1. Interpretation of Results

In this retrospective study, a longer mean OS and CSS occurred in patients who received chemotherapy with clinical stage IB to IIIB. We did not find that there was any OS benefit to the addition of chemotherapy in NSCLC patients with Stage IA disease. This was consistent with the previous LACE meta-analysis that the varied benefit of chemotherapy depended on the disease stage, with the statistically significant improvement in OS for stages II and III but not for stages IA and IB. [23] Given that SEER database is secondary data, there may be

coding errors and result in undercounting patients who received chemotherapy. However, the finding of no benefit to additional chemotherapy for these patients is consistent with other studies.

Different from the findings of STARS-ROSEL trial, which found improved OS for SABR, lobectomy showed the statistically significant benefit of the mean OS with early-stage IA compared to RT group, 33.13 (0.11) vs. 28.22 (0.36), 30.91 (0.19) vs. 23.26 (0.54) with stage IIA, respectively. Chemotherapy with lobectomy contributed to a statistically significant difference in OS compared to the CRT as well. Considering the current cohort included medically inoperable patients in the radiation group, as well as some number of patients who received conventional RT and not SABR (there is a clinical trial that SABR is superior to conventional RT, known as the Space trial, reported by Nyman in 2016).[24]Furthermore, our results were consistent with guideline recommendations from NCCN and ASTRO that treatment is with lobectomy when patients are medically operable.

The previous studies suggested that postoperative chemotherapy or concurrent chemoradiotherapy improve OS for NSCLC patients with stage IB-IIIC. [17] Respectively, in our findings, there was a statistically significant difference in OS between chemotherapy combined with lobectomy and lobectomy group with stage IIB-N1, 30.02 (1.10) vs. 24.29 (1.89), with an even greater difference in CRT vs. RT, 22.71 (2.18) vs. 12.63 (2.18). Chemotherapy improved the OS for patients treated with surgery with stage IIIA-N2, 29.37 (0.60) vs. 22.57 (1.02), compared to the surgery alone, and CRT compared with RT, 21.42 (0.37) vs. 13.07 (0.70), respectively. Therefore, chemotherapy contributed to a better

outcome of OS for patients treated either with surgery or radiation who had stage IB-IIIC disease, compared to surgery or radiation alone.

Interestingly, with stage IIB-IIIC, the group consisting of lobectomy and CRT, did not show any statistical advantage in OS and CSS, compared to the group of the lobectomy combined with chemotherapy. Some researchers have hypothesised that induction CRT increases the rate of negative margins at the time of surgery and negative nodes but does not lead to a survival advantage. [25] Others have thought that CRT can improve survival for patients with more radiosensitive squamous tumors, but not adenocarcinomas. [26] Since the SEERdata published secondary data, as we mentioned above, the data computed from SEER data may include more advanced-stage NSCLC patients in each subgroup compared to the primary data collection. For example, if the initial imaging studies found that a patient had stage IIB (T2N1) disease, but a later diagnostic procedure found N2 involvement (overall stage IIIA), the person could potentially be treated with chemoradiation and miscoded as stage IIB disease.

On multivariate Cox regression analysis (MVA), several confounders suggested an association with HR for each stage, such as undergoing surgery, sex, age, grade, histology, and chemotherapy. It has been acknowledged that histological behavior and grade effect the OS and CSS. Additionally, as we reviewed the cohort diagnosed between 2014 to 2016 among NSCLC patients over 18 years old at diagnosis nationwide, patients below 70 years old with early-stage even Stage IIB were more likely to receive surgical resection, while the distribution was similar in the lobectomy group and SBRT group with advanced-group, instead of receiving RT or CRT treatment. Referring to the previous study, more than half of

elderly patients would consider increasing survival as the primary goal of treatment, even a higher priority than symptom relief during the shared decision-making process. [27] Even though the standard trend towards early-stage NSCLC is lobectomy, considering the poor inoperable candidates with old age and comorbidities, it is often impractical to perform a lobectomy with lymph node sampling on very elderly patients.

Here, the mean CSS in patients with Stage IA between 70-79 years old was around 32.73 (0.18) [95% CI (32.38-33.08)] months and 30.84 (0.24) [95% CI (30.36-31.32)] with Stage IB-IIA, respectively. Worse CSS outcomes were seen for patients age ≥80, which suggests that these patients were receiving substandard therapy compared to younger patients. We also noted that patients treated with radiation were much more likely to be older than age 80, which suggests that patients treated with radiation were more likely to have more medical comorbidities compared to the surgical cohort. As often happens, patients who have many medical comorbidities are treated with radiation because they are medically inoperable. [28]

Historically, the NSCLC incidence rate was higher among men because of a higher smoking rate among men. [29] As smoking rates have decreased drastically over the past 50 years, gender differences among patients with NSCLC have decreased. Overall, we found that women were more likely than men to receive surgical resection with lobectomy, which might contribute to a better mean CSS for NSCLC patients with locally advanced-stage, 25.65 (0.38) [95% CI (24.91-26.39)] in female vs. 22.85 (0.37) [95% CI (22.12-23.58)] in

male. Additionally, the subtype of the squamous cells lung cancer might result in poor prognosis, which happened more often in males than females.

2. Limitation

Compared to RT group, patients who received lobectomy intervention had a statistical survival advantage. Unlike randomized clinical trials, this retrospective study tends to be vulnerable to confounders because of the unknown factors. Large databases can't record the severity of medical conditions, such as the SEER database, showing difficulty in adjusting for the particularly poor health in the cohort. The propensity matching seems technically feasible. In theory this statistical technique results in a "balanced" population, however, in the current study, there is concern about selection bias, since many patients receiving SBRT are medically inoperable, and hence have no exact counterpart in the surgery cohort. [30]

Though this retrospective analysis didn't pair patients via the propensity score, to minimize the selection bias and increase the validity of the cohort, we compared different intervention groups with the same TNM stage. The adjusted Cox proportional hazards regression model accounted for all available covariables that may contribute to prognosis. [31][32] Some medically inoperable patients are certainly included in the RT cohort, which then results in worse overall outcomes for that group. Due to the limitation among cancer-registry studies, we could not obtain disease recurrence data, which would be important for follow up studies.

Overall, our study did contribute to the determination of clinical effectiveness of definitive treatment for non-small cell lung cancer (NSCLC). We performed a comparative

effectiveness study between surgical resection and radiation therapy (stereotactic body radiation (SBRT) for early-stage patients). Our results support the current consensus guidelines for the recommendation of surgical resection for patients with NSCLC where surgery may be feasible. In early stage patients, this means that when medical comorbidities and lung function permit, surgery should be pursued as the initial therapy. We also found that patients with large primary tumors (T2 or greater) benefited from additional chemotherapy following surgical resection. For patients with locally advanced disease, the decision for surgical resection requires more careful consideration. In addition to medical comorbidities, a large primary tumor (T4) or advanced nodal involvement (N3) may make surgery infeasible. For these cases, we found that trimodality therapy (CRT and surgery) resulted in improved outcomes compared to CRT alone. Thus, this study supports the concept of neoadjuvant chemoradiation, with the goal of reducing disease burden to allow for surgical resection. Of course, further studies are needed to confirm the findings of this study.

V. CONCLUSIONS

The current gold standard of care for early-stage lung cancer is surgical resection. For inoperable patients who are not candidates for surgery due to medical comorbidities, radiation is a reliable option when delivered with stereotactic body radiation (SBRT) technique. To determine the clinical effectiveness of definitive treatment for non-small cell lung cancer and perform a comparative effectiveness study of the different techniques, this study included 20,889 NSCLC patients with clinical stage IA to IIIC from the SEER Database. Overall, surgical resection with lobectomy was associated with a significantly improved OS and CSS compared to stereotactic body radiotherapy across disease stages. Multivariable analysis adjusting for confounders such as age, sex, grade, histology, and chemotherapy use.

In terms of the future studies, we would compare a historical cohort of patients diagnosed between 2004 to 2006 to the current result. More specific comparisons via potential confounding variables will explore the natural association with outcomes in NSCLC, both from the surgical and demographic characteristic standpoint, including cigarette smoking, income and education level, and rural/urban status. A propensity-score matching group analysis consisting of a smaller cohort will compare the OS and CSS outcomes.

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