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Survival Impact of Post-Operative Therapy Modalities According to Margin Status in Non-Small Cell Lung Cancer patients in the United States

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Abstract [249 Words]

Objective

Unlike complete (R0) resection guidelines, current National Comprehensive Cancer Network (NCCN) adjuvant therapy guidelines after incomplete (R1/R2) resection of non-small cell lung cancer (NSCLC) are based on low-level evidence. We attempted to validate them.

Methods

Patients with pathologic stage I-IIIA NSCLC from 2004-2011 in the National Cancer Data Base were stratified by margin status, NCCN-specified stage groupings and adjuvant therapy exposure (none, radiotherapy, chemotherapy or both). Five-year overall survival (OS) and hazard ratios, adjusted for patient and institutional characteristics, were compared. We used a parallel analysis of R0 resections to validate our methodology.

Results

We analyzed 3461 R1/R2, and 78,929 R0 resections. After R0 resection, the NCCN-recommended option was associated with the best survival across all stage groups, supporting our analytic approach. R1/R2 stage IA patients treated with radiation had a 26% OS, compared to 58% with no treatment (p=0.003). In stage IB/IIA(N0) R1/R2 patients, radiation was associated with a 25% OS compared to 47% with no treatment (p=0.025) and 62% with chemotherapy (p<0.007). Chemoradiation was not associated with a survival benefit in either group. Patients with IIA (N1)/IIB and IIIA had better

survival with chemotherapy or chemoradiation. No group had a survival benefit with radiation alone.

Conclusions

NCCN adjuvant therapy guidelines after complete resection, based on high-level evidence, are validated, but not guidelines for patients with incompletely resected early stage NSCLC, which are based on low-level evidence. Monomodality postoperative radiotherapy was not validated for any stage. Specific studies are needed to determine optimal management after incomplete resection.

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Perspective Statement

NCCN guidelines for post-operative chemotherapy and radiation after complete surgical resection for NSCLC, based on high-level evidence, are validated in this analysis. Current guidelines for post-operative therapy after incomplete resection of stage I-II NSCLC, which are based on lower-level evidence, are not supported by this analysis.

Central Message

NCCN guidelines for post-operative therapy after incomplete surgical resection in stage I-II patients should be prospectively evaluated.

Abbreviations	
National Comprehensive Cancer Network	NCCN
Postoperative radiotherapy	PORT
Randomized clinical trials	RCTs
Non-small-cell lung cancer	NSCLC
National Cancer Database	NCDB
Interquartile range	IQR
Overall survival	OS
Hazard Ratio	HR

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Introduction

Lung cancer accounts for approximately 27% of all annual US cancer deaths.[1] Most long-term survivors are among the 29% of patients who have undergone curative-intent surgical resection.[2,3] In high-risk patients, adjuvant chemotherapy [4-6] and/or postoperative radiotherapy (PORT) may improve survival.[7] The quality of evidence for the benefit of these treatments varies by stage and margin status.[7-10]

Randomized clinical trials (RCTs) and a pooled analysis have demonstrated the benefit of adjuvant chemotherapy in completely (R0) resected patients with T-category 2b or more advanced primary tumors, and those with nodal metastasis.[4-6,11] A large meta-analysis showed the harmfulness of PORT in R0-resected patients without mediastinal nodal metastasis[12,13]; a retrospective analysis of the US Surveillance, Epidemiology and End Results database and an unplanned retrospective analysis of a clinical trial suggest R0 patients with mediastinal nodal metastasis may benefit from PORT.[7,10]

Unlike the situation after complete resection, there is no RCT evidence to guide adjuvant management for the 2-17% of non-small-cell lung cancer (NSCLC) resections with microscopic (R1) or macroscopic (R2) positive margins.[14-16] However, recipients of incomplete resection are at significantly high risk for early death, irrespective of stage.[16-18] Current National Comprehensive Cancer Network (NCCN) guideline recommendations for post-operative management of these patients are based on unverified expert opinion.[19] Therefore, the guidelines need validation.

We evaluated the survival impact of four different adjuvant therapy options, after incomplete resection, in the National Cancer Database (NCDB) to determine which options seemed best for patients grouped into stage clusters as in the NCCN guidelines.[19]

Methods

Cohort selection. We used the NCDB, an oncology database sourced from Commission on Cancer-accredited facilities, which covers approximately 70% of newly diagnosed US cancer cases.[20,21] We selected patients with surgically resected pathologic stage I-IIIA NSCLC from 2004-2011 (International Classification of Disease for Oncology, 9th edition [ICD-9-CM] site codes C34.0 – C34.9), excluding patients with missing information on last date of contact, administration (or date of administration) of radiation or chemotherapy, facility or patient location. We also excluded patients with more than one surgical procedure, neoadjuvant radiation or chemotherapy, no (or unknown) nodal examination, adjuvant therapy more than 180 days past date of diagnosis, government insurance and death within 60 days of surgery.

Objectives. The primary objective of this analysis was to compare stage-specific survival between post-operative therapy modalities in patients with incomplete surgical resection (R1/R2) who did not undergo re-resection. We used a parallel analysis of R0 patients to evaluate whether our data and methodology produced results congruent with existing high-level evidence for treatment of R0 patients.

Adjuvant therapy options. We classified post-operative therapy modalities as chemotherapy, radiotherapy, chemoradiation, or no treatment. Therapy administered

within six months after surgery, at any dose level, was included as post-operative therapy. The median time from surgery to onset of treatment, by modality, is reported in Supplemental Table I. For combined modality chemoradiation therapy, the second modality had to begin within 2 months of the end of the first. The time from surgery to initiation of adjuvant therapy was evaluated to verify that adjuvant modalities were not typically used for the purpose of salvage therapy in this cohort.

NCCN stage groups and adjuvant therapy guidelines. NCCN recommendations for adjuvant therapy are based on pathologic stage, categorized into the following four groups: 1. Stage IA (T1ab, N0); 2. Stage IB (T2a, N0) and Stage IIA (T2b, N0); 3. Stage IIA (T1ab-T2a, N1) and Stage IIB (T3, N0; T2b N1); 4. Stage IIIA (T1-3, N2; T3, N1). The NCCN-recommended non-surgical adjuvant therapy for group 1 is PORT; for group 2, PORT with or without chemotherapy; for groups 3 and 4, chemoradiation (sequential or concurrent) for R1 and concurrent chemoradiation for R2.[19]

Variables. Margin status was evaluated as negative (R0) or positive (R1, R2 or positive not otherwise specified), and in subsequent analyses R1 and R2 were evaluated individually. Covariates (detailed in Table 1 and Supplemental Table I) in the analysis included patient demographic (age, sex, race, insurance status, income, rural/urban residence, census region), and clinical characteristics (number of comorbidities [0,1, or ≥2], histology, tumor grade, tumor size, primary site, type of surgery), as well as institutional characteristics (facility type).

Statistical Analysis

Overall survival (OS) times were taken from the date of surgery until the date of death or last follow-up. Survival analyses were conducted to compare the four post-operative treatment modalities within each of the four stage groups. OS was estimated using the Kaplan-Meier method and post-operative treatment groups were compared using the log-rank test.

OS comparisons were also evaluated using univariate Cox proportional hazards models and multiple variable Cox proportional hazards models to adjust for covariates. Model-based hazard ratio estimates are reported with 95% confidence intervals. For each model we present unadjusted hazard ratios and hazard ratios adjusted for demographic, clinical, surgical, and institutional characteristics. The proportional hazards assumption was evaluated graphically, using log(-log) survival plots by treatment group. We used 'no adjuvant treatment' as the reference adjuvant therapy option, since there is no clinical trial evidence to support adjuvant therapy after incomplete NSCLC resection. P-values less than 0.05 were considered statistically significant with no adjustment for multiple comparison and all analyses were conducted in SAS Version 9.4 (Cary, NC). [22]

Sensitivity Analyses. We conducted multiple sensitivity analyses to address specific details of the analysis. First, the specific type of positive resection (R1 or R2) was unknown for some margin-positive patients. We evaluated the sensitivity of our results

to margin-positivity of unknown type by conducting multiple analyses in which we grouped them as R1, R2, and eliminated them.

Additional sensitivity analyses were conducted to evaluate if departures from proportional hazards or the large number of covariates adjusted for in each model could impact the observed results from primary analysis. In these analyses, propensity-score adjusted models were used to control for demographic, clinical, surgical, and institutional characteristics with a propensity score, which was entered into the model as a covariate.[23]

Finally, we evaluated the potential impact of departures from the proportional hazards assumption by re-evaluating the multiple variable Cox models after eliminating any exposure groups where the assumption was questionable.

Results

A total of 82,440 patients were eligible: 3461 (4%) with incomplete resection, the primary analysis group of interest (Figure 1), and 78,979 (96%) with R0 resection (Supplemental Figure I), used to validate our analytic approach. The demographic and clinical characteristics of these patients, stratified by NCCN stage group (Table 1A [non-R0] and Supplemental Table IIA [R0]) and adjuvant therapy exposure (Table 1B [non-R0] and Supplemental Table IIB [R0]), are presented.

Early-stage patients with incomplete resection: NCCN groups 1 and 2. OS estimates were compared by treatment modality in margin-positive patients with stage IA (T1ab, N0) and stages IB/IIA (T2a, N0 and T2b, N0). Margin-positive stage IA patients who received PORT alone had significantly lower OS compared to those with no treatment (5-Year OS: 26% vs. 58%, p-value=0.0030, Table 2, Figure 2A). This result trended towards statistical significance in the fully adjusted model (aHR: 1.7, p-value=0.0551, Table II). Similarly, for stage IB/IIA patients, the 5-year OS was 47% with no treatment, and 25% with PORT (p-value=0.0251; aHR 1.28, p-value=0.12) (Table 2, Figure 2B).

We found no significant association between chemotherapy and survival in stage IA patients with positive margins. However, survival was significantly higher in persons with stages IB-IIA who received post-operative chemotherapy compared to no treatment (5-Year OS: 62% vs. 47%, p-value=0.0065, Table 2, Fig 2B). These results remained statistically significant in fully-adjusted models (aHR 0.58, p-value=0.0040, Table 2). Sensitivity analysis using propensity score-adjusted models (Supplemental Table III) and those that did not consider treatment groups where the proportional hazards assumption may be violated (Supplemental Table IV) provided consistent results. Survival with chemoradiation was not significantly different from no adjuvant treatment in group 1 or 2 patients (Table 2).

Late-stage patients with incomplete resection: NCCN groups 3 and 4. In margin-positive NCCN group 3, patients with Stage IIA (T1ab-T2a, N1) or Stage IIB (T3, N0;T2b N1), those who received radiation had a similar survival experience to those who received no

247 treatment (5-Year OS: 26% vs. 27%, p-value= 0.59, Figure 2C, Table 2). Recipients of
248 chemotherapy or chemoradiation had superior survival (p-values<0.0010, Table 2,
249 Figure 2C). Results were similar in fully adjusted models, where the chemotherapy
250 group had 0.72 times the hazard of death compared to no treatment (p-value=0.0041),
251 and the chemoradiation group had 0.74 times the hazard of death (p-value=0.0083).
252
253 Subsequent analysis found no substantial differences in survival in the chemoradiation
254 group based on the order in which therapies were administered (Supplemental Table
255 V). When evaluated separately, patients receiving chemotherapy first and then
256 radiation had 37% 5-Year OS compared to 36% for patients receiving radiation first and
257 then chemotherapy and 38% for those receiving both concurrently (Supplemental Table
258 V).
259
260 Consistent with NCCN guidelines, margin-positive patients with stage IIA or stage IIB
261 were further delineated based on the specific type of incomplete resection, R1, R2, or
262 unknown (margin-positive, but type not specified). Although potentially limited by
263 smaller sample sizes, results were largely consistent with those observed for all margin-
264 positive patients combined (Supplemental Table VI).
265
266 In margin-positive NCCN group 4, patients with Stage IIIA (T1-3, N2; T3, N1), 5-year
267 OS was similar between patients who received PORT (10%) and no treatment (12%, p-
268 value=0.52, Fig 2d). However, compared with no treatment, patients with
269 chemotherapy alone had higher 5-year OS (21% vs. 12%, p-value=0.0045), as did

those with chemoradiation (25%, p-value <0.0001). Fully adjusted models confirmed these findings (Table 2). Specifically, the patients had a lower hazard of death in both the chemotherapy group (aHR=0.77, p-value= 0.0466) and the chemoradiation group (aHR 0.63, p-value <0.0001), compared to no treatment.

Analysis of margin-positive patients with stage IIIA, after further stratification into R1 or R2 subsets, yielded similar results to the combined cohort (Supplemental Table VI). Similar to group 3 patients, we found no meaningful difference in survival in Stage IIIA patients based on the order that chemoradiation was received (Supplemental Table V).

Validation analysis with margin-negative resections. We applied the same analysis to the R0 resection cohort in a parallel analysis. Five-year OS, unadjusted proportional hazards models, and adjusted proportional hazards models in this cohort are presented in Table 3 and Supplemental Figure II. We further delineated the stage IIIA margin-negative survival analysis by pN-category (N0/N1 vs. N2) to match the NCCN guidelines subsets and evaluated their comparative OS based on adjuvant therapy exposure (Supplemental Table VII). The pattern of adjuvant therapy benefit in our analysis matched up with the evidence-based NCCN guidelines for R0 resection (Table 4).

Comparison with NCCN Recommendations Results from margin-positive and margin-negative analyses by stage groups are summarized qualitatively in Table 4, and are compared with the current NCCN recommendations.

Discussion

We compared OS between post-operative adjuvant therapy modalities in patients with completely and incompletely resected NSCLC, to determine if current NCCN recommendations are supported by a robust nationally-representative dataset. Our primary interest was in the patients with incomplete resection, but we used the R0 cohort to validate our methodology, and the suitability of the NCDB for this purpose. This analysis consistently corroborated NCCN guidelines backed by high-level clinical trial evidence, but did not support current recommendations in several scenarios after incomplete resection, where the available evidence is sparse.

In patients with completely resected stage IA NSCLC, RCT have shown no benefit from adjuvant therapy.[4,6] In stage IB-IIB, RCTs and a pooled analysis including the five largest studies, have shown an increase in overall and relapse-free survival with post-operative Cisplatin-based chemotherapy compared to observation.[4-6,11] Our analysis of the R0 cohort is consistent with this evidence. Specifically, patients with completely resected stage IB-IIA NSCLC who received chemotherapy had results superior to all other treatment groups. In patients with completely resected stage IIIA NSCLC, current evidence supports chemotherapy for those with N0 or N1, and chemotherapy or chemoradiation for those with N2, which is the current NCCN recommendation.[19] The R0 cohort analysis supports the use of chemotherapy in N0 and N1 patients, and chemotherapy with or without radiation in patients with N2.

Incomplete resections occur relatively infrequently, and adjuvant therapy trials specifically exclude these patients.[4-7,10,11,24] Therefore, there is no definitive evidence on the best choice of post-operative therapy in this situation.[16-18] NCCN guidelines currently recommend PORT for group 1 (stage IA), PORT with or without chemotherapy for group 2 (stage IB and IIA), and chemoradiation for groups 3 (stage IIA with N1 and IIB) and 4 (T3N1 and T1-3,N2).[19] Our analysis supports observation for group 1, chemotherapy only for group 2, chemotherapy with or without radiation for group 3, and chemoradiation therapy for group 4. This analysis supports the NCCN recommendations for groups 3 and 4, but suggests that the current recommendations may be harmful to patients in groups 1 and 2. It also does not support the use of PORT alone in any subset.

Recent publications using the NCDB have provided conflicting results on the value of PORT after incomplete resection. Hancock found that chemotherapy or chemotherapy plus PORT provided superior results for stages I-III.[18] However patients who received PORT alone after incomplete resection had unimproved (stage II-III) or worse (stage I) survival. Wang reported slightly longer survival in patients completing a full regime of PORT at 50-74 Gy post-operatively.[25] Key differences in our study may explain the conflicting results.

Our analysis of the NCDB used the NCCN adjuvant therapy stage groupings in an attempt to validate the treatment guidelines. Therefore, we further delineated stage I patients by pT-category and stage IIA patients by pN-category. This delineation,

coupled with the broader timeline (2004-2011 vs. 2003-2006), may explain the subtle difference between our findings and those of Hancock.[18] Both studies found that early-stage patients receiving PORT alone had shorter survival. However, we found the best survival for early-stage (NCCN group 2) patients was with chemotherapy alone compared with Hancock's findings that chemotherapy with or without PORT both showed similar survival that was superior to no adjuvant treatment or PORT alone for the undilineated group of stage II and III patients.[18]

The report by Wang, supporting the use of PORT in Stage II-III patients with incomplete resection, differed from our work by evaluating only patients with an optimal PORT experience.[25] Specifically, Wang excluded all patients who died within 120 days of surgery, and only included patients who completed optimal-dose radiation. A less optimal classification of PORT use is more pragmatic and provides better information for treatment of patients, whose ability to receive a full treatment regime of PORT cannot be known at the time of treatment decision. Patients who died as a result of acute radiation complications would have been excluded from their analysis. Another difference is that they treated chemotherapy as a confounding variable rather than a separate treatment option as we, and Hancock, have done.

Our PORT analysis group included all persons who survived 60 days post-surgery and received treatment with PORT within 6 months of surgery. Patients who discontinued PORT or received PORT at a less-than-optimal dose were included to adhere to the intention-to-treat principle and avoid potential selection bias. Because treatment with

PORT alone may be carried out differently than PORT with chemotherapy, we considered these two treatment options separately to better represent clinical practice and to avoid the potential for residual confounding by controlling for chemotherapy use exclusively through statistical modeling.

This retrospective study has several limitations. We have expressly excluded the primary recommendation of re-resection for non-R0 resections because of the relatively small number of such patients in the database. Ideally, PORT is preferably commenced within 60 days. We used a 6-month eligibility window, as others have done in these types of analyses, to reflect the practical reality that some patients start adjuvant therapy late.[18,25] The median time to onset of PORT alone was 52 days, and 75% of patients initiated therapy within 74 days. This suggests that PORT was used adjuvantly, and not for salvage therapy after disease progression. However, it is impossible to verify the clinical circumstances around any of the treatments.

The NCDB covers 70% of all lung cancer cases in the US, drawing from a diverse group of hospitals. However, results may not apply directly to substantially different institutions. Although the NCDB is thorough, incomplete and inaccurate data are still potential problems. Although we addressed this limitation for critical variables by validating our results with sensitivity analyses, unequal assignment of post-operative treatment modalities may have impacted our results and the sample size of some analysis subsets may be too small for meaningful statistical inference. Outside a well-executed RCT, this remains a potential explanation for differences observed in all

studies of this question. We have addressed this limitation, as well as possible, with extensive adjustment by statistical analysis.

The lack of observed benefit from PORT or chemoradiation in early-stage patients after incomplete resection parallels the current evidence in completely resected patients; the impact of radiation therapy in reducing the increased cancer-related mortality risk after incomplete resection does not seem to overcome the excessive treatment-related mortality risk of PORT.[26] Chemotherapy appears to be valuable to some degree across stage groups; patients with mediastinal nodal metastasis seem to benefit from chemotherapy or combined-modality chemoradiation.

Well-conducted retrospective evaluations can lead to conflicting conclusions based on selection criteria for assigning treatment groups after the fact. An inherent imbalance between treatment groups prior to treatment initiation is likely when treatment is selected based on physician decision after individual patient assessment. Statistical adjustment is unlikely to completely eliminate such confounding-by-indication.

This study provides the most comprehensive evaluation of NCCN guidelines for postoperative therapy to date. Results are largely consistent with high-level evidence available after complete surgical resection. In patients with incomplete resection, where the available evidence is far less, these data did not support the use of PORT in early-stage patients. All available evidence in incompletely-resected patients is lower-level, and results are discrepant. Only RCTs can definitively determine the best adjuvant therapy for incompletely resected NSCLC.

Such a trial will be challenging to execute because of the relatively low incidence of incomplete resections, and the practical reality that incomplete resections are least frequent in the types of institutions that typically conduct clinical trials.[16] However, infrastructure such as the National Cancer Institute's Community Oncology Research Program can be harnessed to support such a trial. The possibility of patient harm in the existing evidence void should stimulate the political will to resolve this question.

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Disclosures

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Figure legends

Figure 1. Study consort diagram for margin positive patients

Figure 2. Kaplan Meier survival curves for margin positive patients categorized by National Comprehensive Cancer Network adjuvant therapy stage groups. The log-rank p-value tests the null hypothesis that all 4 groups have similar survival.
a.) Group 1- stage IA (T1ab, N0);
b.) Group 2- stage IB (T2a, N0) and Stage IIA (T2b, N0);
c.) Group 3- stage IIA (T1ab-T2a, N1) and stage IIB (T3, N0; T2b N1);
d.) Group 4- stage IIIA (T1-3, N2; T3, N1).

Central Figure. Kaplan Meier Survival Curves for Margin Positive Patients in Stage IB (T2a, N0) and Stage IIA (T2b, N0).

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Table 1A. Patient Demographic and Institutional Characteristics Among Margin Positive Patients by Stage Group.

Categories	Total	Stage IA(T1ab,N0)	Stage IB (T2a,N0) & IIA (T2b,N0)	Stage IIA(T1ab-T2a,N1) & IIB	Stage IIIA(T1-T3,N2; T3,N1)	p-value
	N=3461	N=369	N=857	N=1317	N=918	
	N (%)	N (%)	N (%)	N (%)	N (%)	
Age Group						
18-49	227 (7)	16 (4)	40 (5)	90 (7)	81 (9)	< .0001
50-64	1190 (34)	105 (28)	247 (29)	476 (36)	362 (39)	
65-74	1230 (36)	141 (38)	328 (38)	458 (35)	303 (33)	
75-90	814 (24)	107 (29)	242 (28)	293 (22)	172 (19)	
Sex						
Male	1851 (53)	159 (43)	436 (51)	766 (58)	490 (53)	< .0001
Female	1610 (47)	210 (57)	421 (49)	551 (42)	428 (47)	
Race/Ethnicity						
Non-Hispanic, White	2653 (77)	287 (78)	670 (78)	1000 (76)	696 (76)	0.2
Hispanic	73 (2)	10 (3)	14 (2)	27 (2)	22 (2)	
Black	342 (10)	39 (11)	79 (9)	123 (9)	101 (11)	
Other	88 (3)	6 (2)	16 (2)	48 (4)	18 (2)	
Missing	305 (9)	27 (7)	78 (9)	119 (9)	81 (9)	
Insurance						
Uninsured	87 (3)	6 (2)	19 (2)	40 (3)	22 (2)	< .0001
Medicaid	176 (5)	15 (4)	36 (4)	63 (5)	62 (7)	
Younger Medicare	219 (6)	22 (6)	42 (5)	74 (6)	81 (9)	
Older Medicare	1758 (51)	221 (60)	497 (58)	635 (48)	405 (44)	
Private	1184 (34)	103 (28)	257 (30)	485 (37)	339 (37)	
Missing	37 (1)	2 (1)	6 (0)	20 (2)	9 (1)	
Median Income-Quartile						
<$30,000	478 (14)	52 (14)	117 (14)	180 (14)	129 (14)	0.84
$30,000- $34,999	708 (20)	67 (18)	175 (20)	276 (21)	190 (21)	
$35,000- $45,999	999 (29)	100 (27)	242 (28)	382 (29)	275 (30)	
$46,000+	1095 (32)	126 (34)	275 (32)	407 (31)	287 (31)	
Missing	181 (5)	24 (7)	48 (6)	72 (5)	37 (4)	
Comorbidity						
0	1611 (47)	144 (39)	387 (45)	623 (47)	457 (50)	0.014
1	1270 (37)	149 (40)	321 (37)	491 (37)	309 (34)	
2+	580 (17)	76 (21)	149 (17)	203 (15)	152 (17)	
Histology						
NOS	9 (0)	1 (0)	1 (0)	7 (1)	0 (0)	< .0001
Large Cell	177 (5)	14 (4)	34 (4)	70 (5)	59 (6)	
Squamous	1340 (39)	121 (33)	335 (39)	572 (43)	312 (34)	
Other	248 (7)	16 (4)	49 (6)	110 (8)	73 (8)	
Adenocarcinoma	1687 (49)	217 (59)	438 (51)	558 (42)	474 (52)	
Tumor Grade						
well/moderately differentiated	1688 (49)	244 (66)	477 (56)	579 (44)	388 (42)	< .0001
poorly/undifferentiated	1641 (47)	105 (28)	343 (40)	695 (53)	498 (54)	
Unknown	132 (4)	20 (5)	37 (4)	43 (3)	32 (3)	
Tumor Size						
≤3cm	1339 (39)	356 (96)	279 (33)	418 (32)	286 (31)	< .0001
>3cm-≤5cm	1156 (33)	3 (1)	367 (43)	457 (35)	329 (36)	
>5cm	940 (27)	8 (2)	207 (24)	428 (33)	297 (32)	
Unknown	26 (1)	2 (1)	4 (0)	14 (1)	6 (1)	
Rural/Urban						
Rural	664 (19)	65 (18)	165 (19)	263 (20)	171 (19)	0.46
Urban	2582 (75)	279 (76)	631 (74)	970 (74)	702 (76)	
Unknown	215 (6)	25 (7)	61 (7)	84 (6)	45 (5)	
Census Region						

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Northeast	572 (17)	72 (20)	136 (16)	207 (16)	157 (17)	0.58
Midwest	1100 (32)	108 (29)	283 (33)	409 (31)	300 (33)	
South	1366 (39)	150 (41)	327 (38)	532 (40)	357 (39)	
West	423 (12)	39 (11)	111 (13)	169 (13)	104 (11)	
Primary Site						
C340- Main bronchus	54 (2)	1 (0)	13 (2)	15 (1)	25 (3)	< .0001
C341-upper lobe	2068 (60)	224 (61)	474 (55)	854 (65)	516 (56)	
C342-Middle lobe	174 (5)	22 (6)	54 (6)	46 (3)	52 (6)	
C343-Lower lobe	976 (28)	113 (31)	278 (32)	335 (25)	250 (27)	
C348-Overlapping lesion	124 (4)	3 (1)	28 (3)	40 (3)	53 (6)	
C349-Lung NOS	65 (2)	6 (2)	10 (1)	27 (2)	22 (2)	
T category						
T1	676 (20)	369 (100)	0 (0)	184 (14)	123 (13)	< .0001
T2	1773 (51)	0 (0)	857 (100)	536 (41)	380 (41)	
T3	1012 (29)	0 (0)	0 (0)	597 (45)	415 (45)	
N Category						
N0	1823 (53)	369 (100)	857 (100)	597 (45)	0 (0)	< .0001
N1	964 (28)	0 (0)	0 (0)	720 (55)	244 (27)	
N2	674 (19)	0 (0)	0 (0)	0 (0)	674 (73)	
Surgery						
Sublobar	420 (12)	114 (31)	95 (11)	109 (8)	102 (11)	< .0001
Lobe/bilobectomy	2643 (76)	250 (68)	703 (82)	1060 (80)	630 (69)	
Pneumonectomy	398 (12)	5 (1)	59 (7)	148 (11)	186 (20)	
Facility type						
Community Cancer Program	329 (10)	31 (8)	75 (9)	139 (11)	84 (9)	0.75
Comprehensive Community Cancer Program	1772 (51)	191 (52)	445 (52)	679 (52)	457 (50)	
Teaching/Research Cancer Program	738 (21)	79 (21)	188 (22)	274 (21)	197 (22)	
NCI Program/Network	299 (9)	39 (11)	72 (8)	104 (8)	84 (9)	
Other	323 (9)	29 (8)	77 (9)	121 (9)	96 (10)	

Table 1B. Patient Demographic and Institutional Characteristics Among Margin Positive Patients by Adjuvant Therapy.

Categories	Total	No Treatment	Chemotherapy	Radiation therapy	Chemoradiation	p-value
	N=3461	N=1406	N=645	N=447	N=963	
	N (%)	N (%)	N (%)	N (%)	N (%)	
Stage Group						
Stage IA	369 (11)	265 (19)	19 (3)	60 (13)	25 (3)	< .0001
Stage IB & IIA	857 (25)	477 (34)	142 (22)	119 (27)	119 (12)	
Stage IIA & IIB	1317 (38)	419 (30)	284 (44)	199 (45)	415 (43)	
Stage IIIA	918 (27)	245 (17)	200 (31)	69 (15)	404 (42)	
Age Group						
18-49	227 (7)	66 (5)	44 (7)	14 (3)	103 (11)	< .0001
50-64	1190 (34)	390 (28)	271 (42)	106 (24)	423 (44)	
65-74	1230 (36)	508 (36)	227 (35)	170 (38)	325 (34)	
75-90	814 (24)	442 (31)	103 (16)	157 (35)	112 (12)	
Sex						
Male	1851 (53)	735 (52)	337 (52)	240 (54)	539 (56)	0.31
Female	1610 (47)	671 (48)	308 (48)	207 (46)	424 (44)	
Race/Ethnicity						
Non-Hispanic, White	2653 (77)	1087 (77)	475 (74)	350 (78)	741 (77)	0.18
Hispanic	73 (2)	35 (2)	15 (2)	8 (2)	15 (2)	
Black	342 (10)	147 (10)	67 (10)	34 (8)	94 (10)	
Other	88 (3)	29 (2)	18 (3)	17 (4)	24 (2)	
Missing	305 (9)	108 (8)	70 (11)	38 (9)	89 (9)	
Insurance						

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Uninsured	87 (3)	37 (3)	14 (2)	9 (2)	27 (3)	< .0001
Medicaid	176 (5)	69 (5)	23 (4)	23 (5)	61 (6)	
Younger Medicare	219 (6)	77 (5)	44 (7)	16 (4)	82 (9)	
Older Medicare	1758 (51)	823 (59)	275 (43)	296 (66)	364 (38)	
Private	1184 (34)	388 (28)	281 (44)	96 (21)	419 (44)	
Missing	37 (1)	12 (1)	8 (1)	7 (2)	10 (1)	
Median Income-Quartile						
<$30,000	478 (14)	196 (14)	79 (12)	72 (16)	131 (14)	0.25
$30,000- $34,999	708 (20)	281 (20)	139 (22)	81 (18)	207 (22)	
$35,000- $45,999	999 (29)	405 (29)	171 (27)	132 (30)	291 (30)	
$46,000+	1095 (32)	448 (32)	211 (33)	139 (31)	297 (31)	
Missing	181 (5)	76 (5)	45 (7)	23 (5)	37 (4)	
Comorbidity						
0	1611 (47)	634 (45)	331 (51)	183 (41)	463 (48)	0.005
1	1270 (37)	511 (36)	225 (35)	179 (40)	355 (37)	
2+	580 (17)	261 (19)	89 (14)	85 (19)	145 (15)	
Histology						
NOS	9 (0)	3 (0)	2 (0)	1 (0)	3 (0)	
Large Cell	177 (5)	57 (4)	38 (6)	23 (5)	59 (6)	< .0001
Squamous	1340 (39)	524 (37)	214 (33)	216 (48)	386 (40)	
Other	248 (7)	90 (6)	46 (7)	32 (7)	80 (8)	
Adenocarcinoma	1687 (49)	732 (52)	345 (53)	175 (39)	435 (45)	
Tumor Grade						
well/moderately differentiated	1688 (49)	753 (54)	307 (48)	208 (47)	420 (44)	
poorly/undifferentiated	1641 (47)	590 (42)	312 (48)	221 (49)	518 (54)	< .0001
Unknown	132 (4)	63 (4)	26 (4)	18 (4)	25 (3)	
Tumor Size						
≤3cm	1339 (39)	654 (47)	212 (33)	172 (38)	301 (31)	
>3cm-≤5cm	1156 (33)	417 (30)	223 (35)	161 (36)	355 (37)	< .0001
>5cm	940 (27)	323 (23)	207 (32)	112 (25)	298 (31)	
Unknown	26 (1)	12 (1)	3 (0)	2 (0)	9 (1)	
Rural/Urban						
Rural	664 (19)	285 (20)	110 (17)	90 (20)	179 (19)	0.014
Urban	2582 (75)	1023 (73)	482 (75)	337 (75)	740 (77)	
Unknown	215 (6)	98 (7)	53 (8)	20 (4)	44 (5)	
Census Region						
Northeast	572 (17)	234 (17)	106 (16)	79 (18)	153 (16)	< .0001
Midwest	1100 (32)	386 (27)	222 (34)	144 (32)	348 (36)	
South	1366 (39)	586 (42)	246 (38)	158 (35)	376 (39)	
West	423 (12)	200 (14)	71 (11)	66 (15)	86 (9)	
Primary Site						
C340- Main bronchus	54 (2)	16 (1)	8 (1)	12 (3)	18 (2)	0.22
C341-upper lobe	2068 (60)	825 (59)	384 (60)	280 (63)	579 (60)	
C342-Middle lobe	174 (5)	76 (5)	34 (5)	14 (3)	50 (5)	
C343-Lower lobe	976 (28)	412 (29)	185 (29)	122 (27)	257 (27)	
C348-Overlapping lesion	124 (4)	45 (3)	22 (3)	16 (4)	41 (4)	
C349-Lung NOS	65 (2)	32 (2)	12 (2)	3 (1)	18 (2)	
T category						
T1	676 (20)	368 (26)	82 (13)	89 (20)	137 (14)	< .0001
T2	1773 (51)	757 (54)	388 (60)	191 (43)	437 (45)	
T3	1012 (29)	281 (20)	175 (27)	167 (37)	389 (40)	
N Category						
N0	1823 (53)	912 (65)	247 (38)	309 (69)	355 (37)	< .0001
N1	964 (28)	320 (23)	248 (38)	94 (21)	302 (31)	
N2	674 (19)	174 (12)	150 (23)	44 (10)	306 (32)	
Surgery						
Sublobar	420 (12)	180 (13)	56 (9)	78 (18)	106 (11)	< .0001

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Lobe/bilobectomy	2643 (76)	1077 (77)	482 (75)	335 (75)	749 (78)	
Pneumonectomy	398 (12)	149 (11)	107 (17)	34 (8)	108 (11)	
Facility type						
Community Cancer Program	329 (10)	123 (9)	55 (9)	33 (7)	118 (12)	< .0001
Comprehensive Community Cancer Program	1772 (51)	687 (49)	328 (51)	249 (56)	508 (53)	
Teaching/Research Cancer Program	738 (21)	343 (24)	131 (20)	97 (22)	167 (17)	
NCI Program/Network	299 (9)	133 (9)	66 (10)	32 (7)	68 (7)	
Other	323 (9)	120 (9)	65 (10)	36 (8)	102 (11)	

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Table 2. Kaplan Meier Survival Analysis and Proportional Hazards Models by Stage Group for Margin Positive Patients.

		Margin Positive				
	Post-Op Treatment	**N**	**5 Year Overall Survival (%) (Logrank P-Value*)**	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio** (95% CI)**	**P-Value***
Group 1: Stage IA (T1ab, N0)	No Treatment	265	58 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	19	65 (0.6687)	0.81 (0.35-1.86)	1.27 (0.48-3.38)	0.6369
	Radiation Only	60	26 (0.0030)	1.97 (1.25-3.11)	1.68 (0.99-2.84)	0.0551
	Chemo + Rad	25	35 (0.0895)	1.69 (0.92-3.12)	0.96 (0.47-1.98)	0.9176
Group 2: Stage IB (T2a, N0) & Stage IIA (T2b, N0)	No Treatment	477	47 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	142	62 (0.0065)	0.61 (0.43-0.87)	0.58 (0.40-0.84)	0.004
	Radiation Only	119	25 (0.0251)	1.39 (1.04-1.86)	1.28 (0.94-1.74)	0.1185
	Chemo + Rad	119	39 (0.3571)	1.15 (0.85-1.57)	0.97 (0.70-1.35)	0.8678
Group 3: Stage IIA (T1ab-T2a, N1) & Stage IIB (T3, N0;T2b N1)	No Treatment	419	27 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	284	36 (0.0001)	0.65 (0.53-0.81)	0.72 (0.58-0.90)	0.0041
	Radiation Only	199	26 (0.5907)	1.06 (0.85-1.32)	0.94 (0.74-1.18)	0.5878
	Chemo + Rad	415	37 (<.0001)	0.68 (0.56-0.83)	0.76 (0.62-0.93)	0.0083
Group 4: Stage IIIA (T1-3, N2; T3, N1)	No Treatment	245	12 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	200	21 (0.0048)	0.70 (0.55-0.90)	0.77 (0.60-1.00)	0.0466
	Radiation Only	69	10 (0.5215)	1.11 (0.81-1.51)	1.03 (0.74-1.43)	0.8729
	Chemo + Rad	404	25 (<.0001)	0.59 (0.48-0.72)	0.63 (0.51-0.79)	<.0001

*P-values compare each treatment to referent (no treatment) **Adjusted for Age, Sex, Race/Ethnicity, Insurance, Median Income, Comorbidity, Histology, Tumor Grade, Tumor Size, Rural/Urban, Census Region, Primary Site, T Category, N Category, Surgery Facility type, Facility Surgical % Lung Cancer, Facility % Medicaid or Uninsured

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Table 3. Kaplan Meier Survival Analysis and Proportional Hazards Models by Stage Group for Margin Negative Patients.

		Margin Negative				
	Post-Op Treatment	**N**	**5 Year Overall Survival (%) (log-rank P-Value*)**	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio** (95% CI)**	**P-Value***
Group 1: Stage IA (T1ab, N0)	No Treatment	33780	71 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	789	74 (0.2946)	0.92 (0.78-1.08)	1.02 (0.87-1.20)	0.816
	Radiation Only	136	44 (<.0001)	2.89 (2.22-3.73)	2.18 (1.67-2.85)	<.0001
	Chemo + Rad	76	40 (<.0001)	3.19 (2.21-4.59)	2.99 (2.07-4.31)	<.0001
Group 2: Stage IB (T2a, N0) & Stage IIA (T2b, N0)	No Treatment	19281	57 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	4568	68 (<.0001)	0.68 (0.63-0.72)	0.74 (0.69-0.80)	<.0001
	Radiation Only	250	38 (<.0001)	1.92 (1.60-2.31)	1.8 (1.49-2.16)	<.0001
	Chemo + Rad	215	47 (0.0003)	1.47 (1.19-1.81)	1.41 (1.14-1.74)	0.0016
Group 3: Stage IIA (T1ab-T2a, N1) & Stage IIB (T3, N0;T2b N1)	No Treatment	6101	37 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	5788	53 (<.0001)	0.59 (0.56-0.63)	0.66 (0.62-0.70)	<.0001
	Radiation Only	354	28 (<.0001)	1.35 (1.17-1.57)	1.36 (1.18-1.58)	<.0001
	Chemo + Rad	895	40 (0.1772)	0.93 (0.84-1.03)	1.04 (0.93-1.16)	0.4811
Group 4: Stage IIIA (T1-3, N2; T3, N1)	No Treatment	2119	24 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	2520	39 (<.0001)	0.59 (0.55-0.65)	0.63 (0.58-0.69)	<.0001
	Radiation Only	248	18 (0.0747)	1.18 (0.99-1.39)	1.15 (0.97-1.37)	0.1025
	Chemo + Rad	1859	38 (<.0001)	0.62 (0.57-0.68)	0.69 (0.63-0.76)	<.0001

*P-values compare each treatment to referent (no treatment) **Adjusted for Age, Sex, Race/Ethnicity, Insurance, Median Income, Comorbidity, Histology, Tumor Grade, Tumor Size, Rural/Urban, Census Region, Primary Site, T Category, N Category, Surgery Facility type, Facility Surgical % Lung Cancer, Facility % Medicaid or Uninsured

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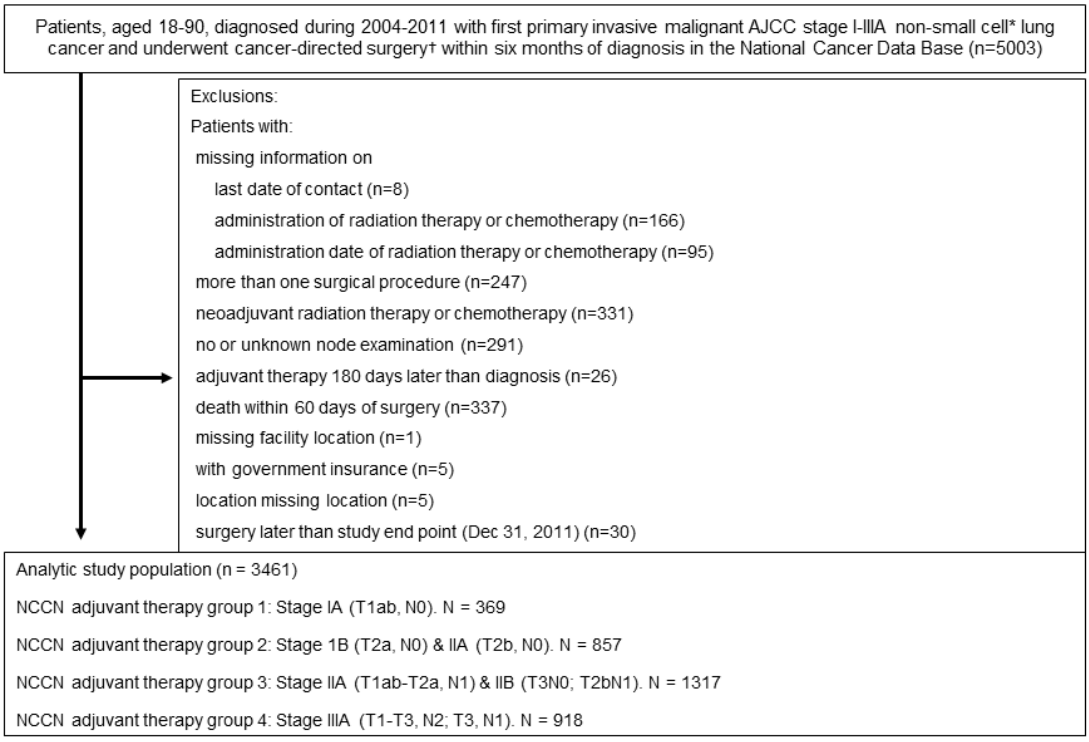
Table 4. Comparative survival impact of post-operative adjuvant therapy in patients with completely and incompletely resected stage I – IIIA NSCLC in the NCDB, current NCCN adjuvant therapy recommendations ('recs'), and objective results from our analysis.

Stage	Margin Status	Chemo	Radiation	chemoXRT	NCCN	NCDB Data
Group 1: Stage IA	Negative	Neutral	Worse	Worse	Observe	Supports observation
	Positive	Neutral	Worse	Neutral	Radiation	Supports Observation
Group 2: Stage IB & Stage IIA	Negative	Better	Worse	Worse	Observe or Chemo	Supports Chemo Only
	Positive	Better	Neutral	Neutral	RT+/-Chemo	Supports Chemo Only
Group 3: Stage IIA & Stage IIB	Negative	Better	Worse	Neutral	Chemo	Supports Chemo Only
	Positive	Better	Neutral	Better		
	R1	Better	Neutral	Better	Chemo+RT	Supports Chemo+/-RT
	R2	Insufficient Data (Supplemental Table I)			Chemo+RT	
Group 4: Stage IIIA	Negative	Better	Neutral	Better		
	Non-N2	Better	Neutral	Neutral	Chemo	Supports chemo only
	N2	Better	Worse	Better	Chemo+RT	Supports Chemo+/-RT
Group 4: Stage IIIA	Positive	Better	Neutral	Better		
	R1	Neutral	Neutral	Better	Chemo+RT	Supports chemo+RT
	R2	Insufficient Data (Supplemental Table I)				

Chemo= chemotherapy; RT= radiation therapy; Chemo+RT= combined-modality chemotherapy and radiation therapy.

Figure 1: Patient selection schema among margin-positive NSCLC patients



*Non-small cell histology was identified through International Classification of Diseases for Oncology, 3rd version (ICD-O-3) histology codes: 8010-8040, 8050 – 8076, 8140, 8143, 8211, 8230-8231, 8246, 8250 – 8260, 8310, 8320, 8323, 8430, 8470 – 8490, 8550 – 8573, 8980, 8981.
†Cancer-directed surgery was identified through site-specific surgical codes (21, 22, 30 – 70), including sub-lobectomy, lobectomy, bi-lobectomy, and pneumonectomy. NCCN = National Comprehensive Cancer Network.

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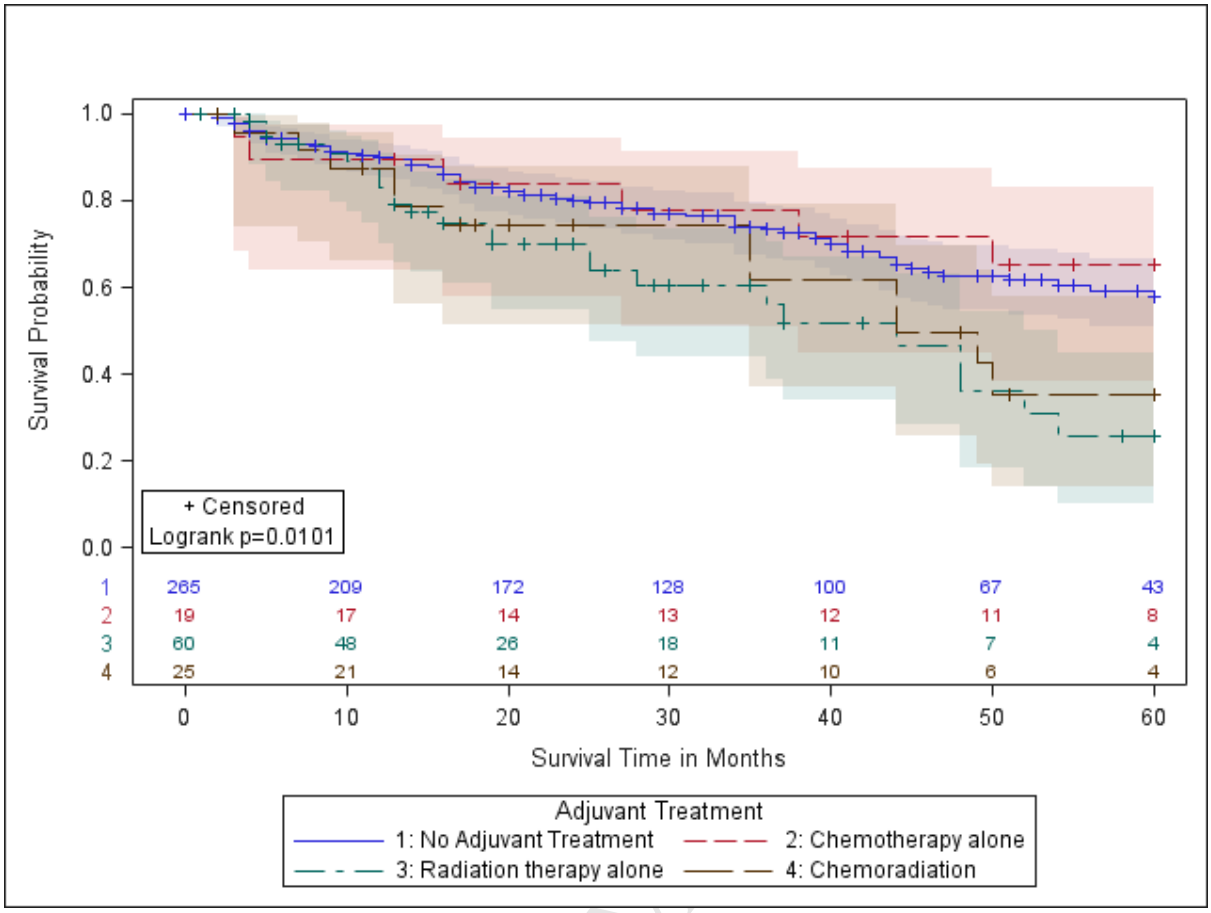

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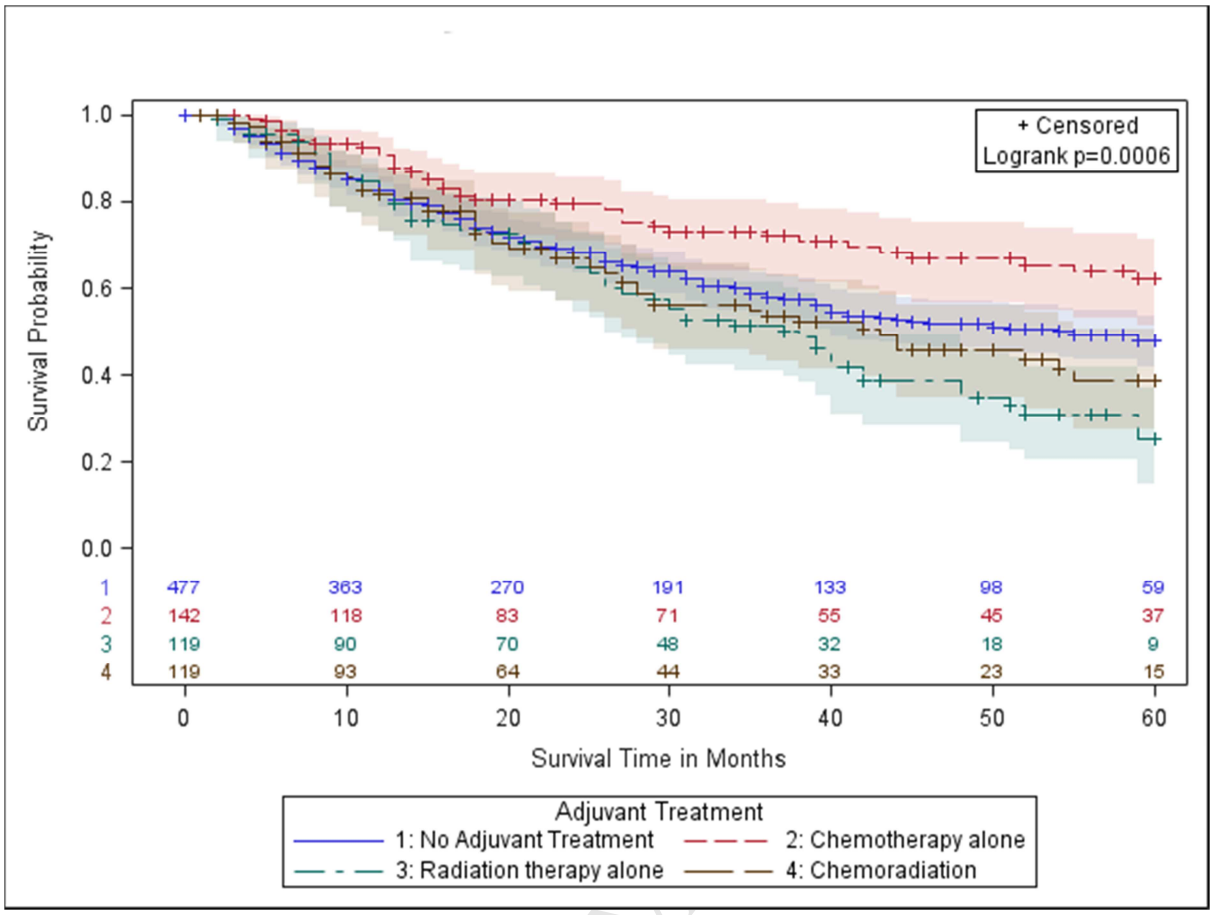

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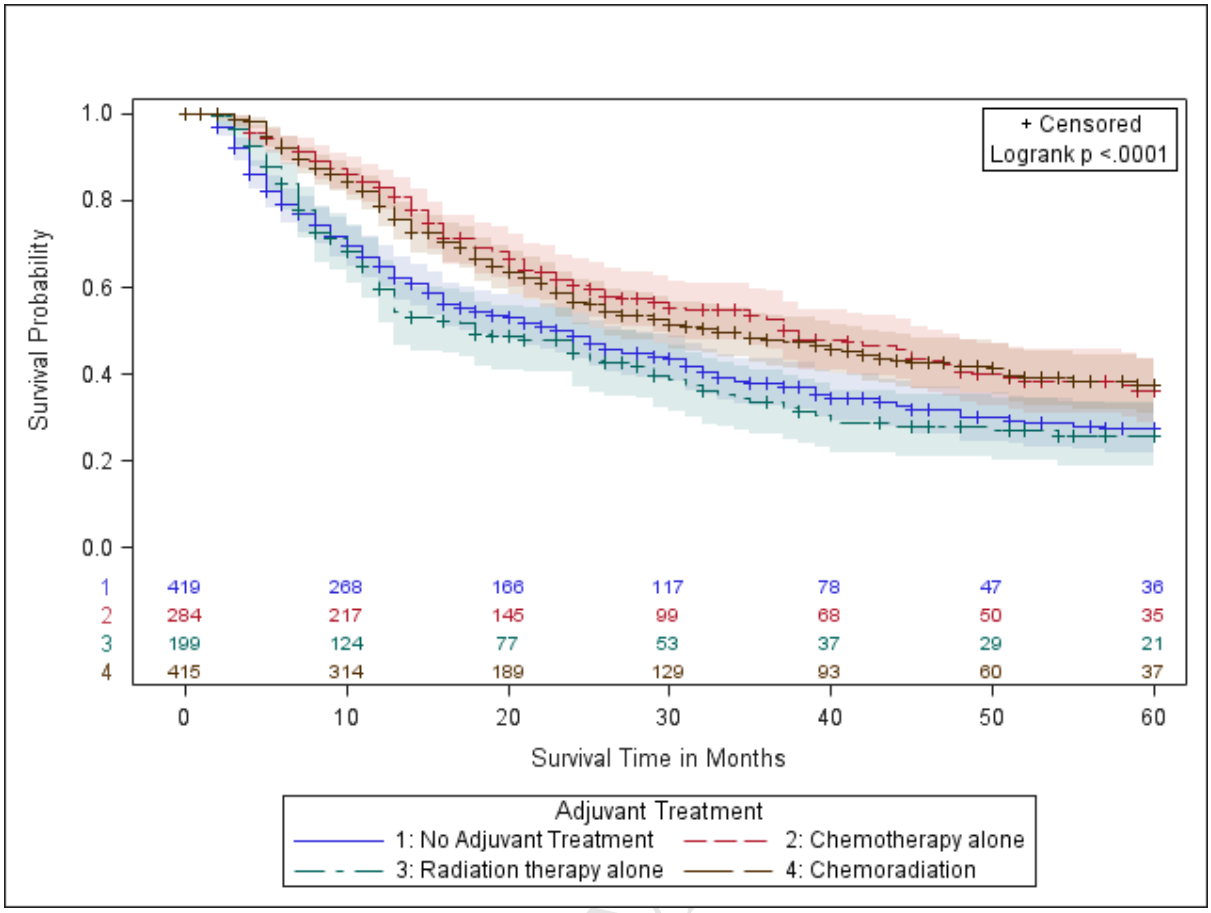

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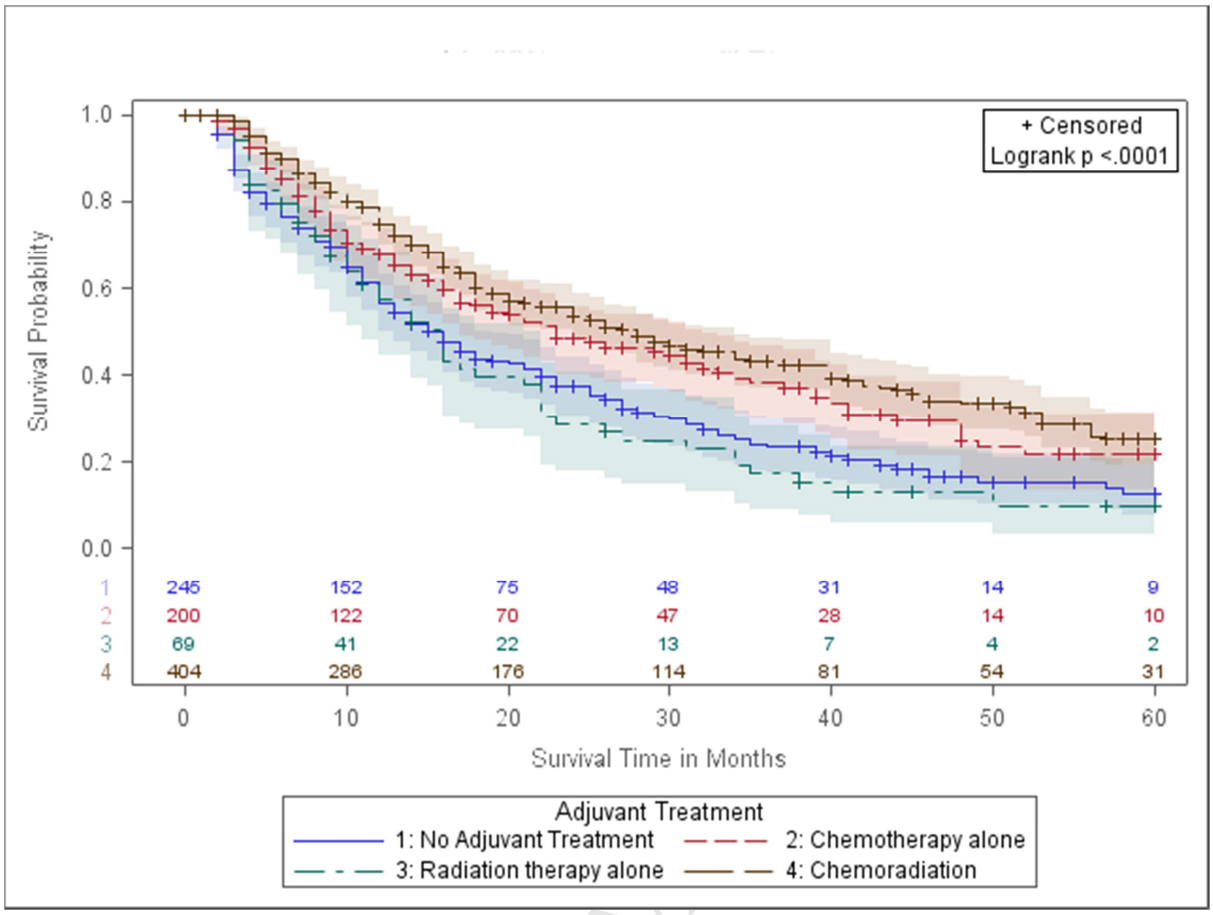

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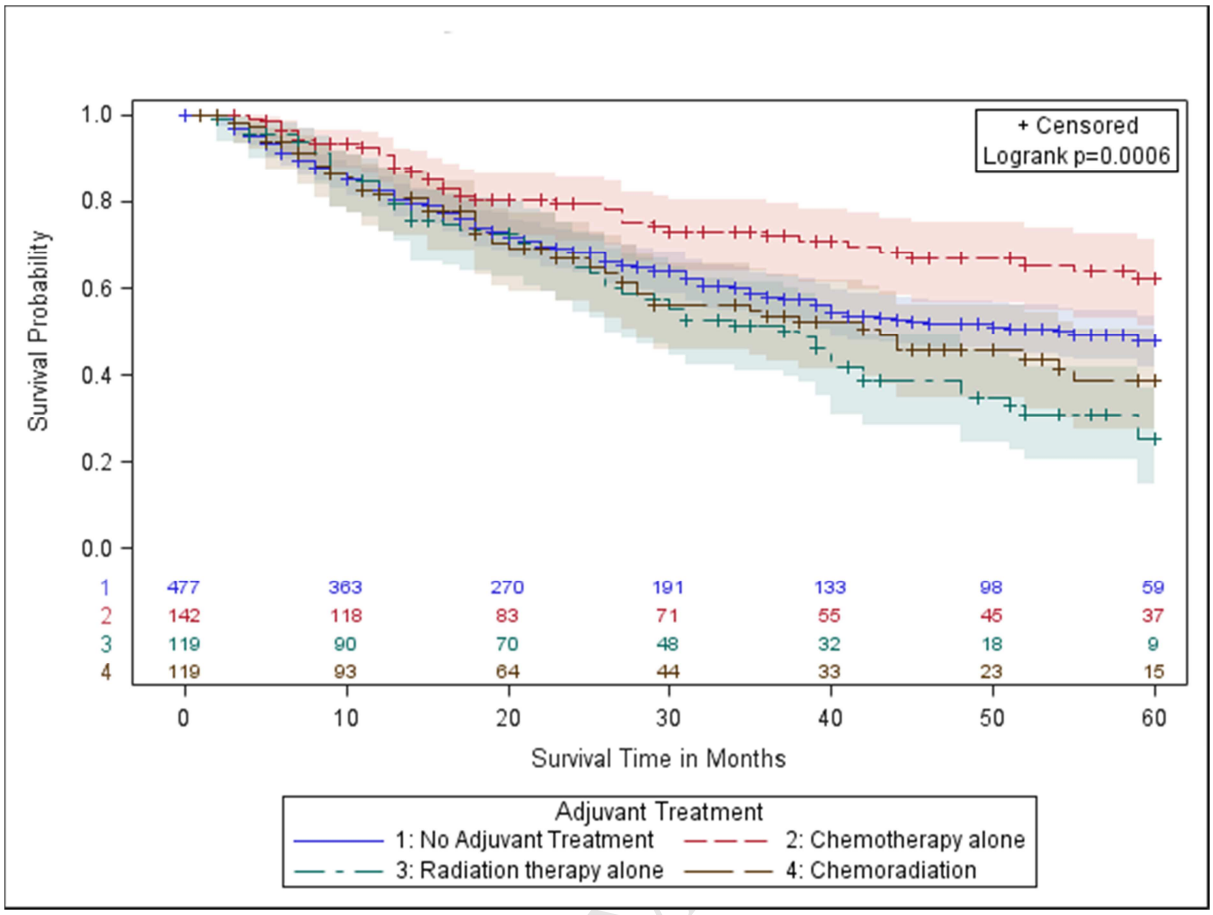

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Supplemental Tables and Figures:

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Supplemental Table I. Times from Surgery to Adjuvant Therapy

	Median	IQR
Days from surgery to initiation of PORT in patients without chemotherapy	52	39-74
Days from surgery to initiation of chemotherapy in patients without PORT	47	35-62
In Patients receiving chemotherapy and PORT		
Days from surgery to initiation of radiation therapy	57	40-126
Days from surgery to initiation of chemotherapy	43	34-58

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Supplemental Table IIA. Patient Demographic and Institutional Characteristics Among Margin Negative Patients by Stage Group.

Categories	Total	Stage IA(T1ab,N0)	Stage IB (T2a,N0) & IIA (T2b,N0)	Stage IIA(T1ab-T2a,N1) & IIB	Stage IIIA(T1-T3,N2; T3,N1)	p-value
	N=78979 N (%)	N=34781 N (%)	N=24314 N (%)	N=13138 N (%)	N=6746 N (%)	
Age Group						
18-49	4389 (6)	1870 (5)	1181 (5)	820 (6)	518 (8)	< .0001
50-64	25864 (33)	11380 (33)	7352 (30)	4651 (35)	2481 (37)	
65-74	29782 (38)	13462 (39)	9084 (37)	4871 (37)	2365 (35)	
75-90	18944 (24)	8069 (23)	6697 (28)	2796 (21)	1382 (21)	
Sex						
Male	37844 (48)	14933 (43)	12480 (51)	7055 (54)	3376 (50)	< .0001
Female	41135 (52)	19848 (57)	11834 (49)	6083 (46)	3370 (50)	
Race/Ethnicity						
Non-Hispanic, White	61957 (79)	27532 (79)	18978 (78)	10303 (78)	5144 (76)	< .0001
Hispanic	1734 (2)	709 (2)	565 (2)	278 (2)	182 (3)	
Black	6478 (8)	2665 (8)	2029 (8)	1124 (9)	660 (10)	
Other	2078 (3)	879 (3)	657 (3)	322 (3)	220 (3)	
Missing	6732 (9)	2996 (9)	2085 (9)	1111 (9)	540 (8)	
Insurance						
Uninsured	1517 (2)	563 (2)	493 (2)	286 (2)	175 (3)	< .0001
Medicaid	3325 (4)	1301 (4)	1030 (4)	635 (5)	359 (5)	
Younger Medicare	4538 (6)	2120 (6)	1278 (5)	745 (6)	395 (6)	
Older Medicare	41134 (52)	18298 (53)	13253 (55)	6452 (49)	3131 (46)	
Private	27402 (35)	12033 (35)	7946 (33)	4828 (37)	2595 (39)	
Missing	1063 (1)	466 (1)	314 (1)	192 (2)	91 (1)	
Median Income-Quartile						
<$30,000	10308 (13)	4326 (12)	3287 (14)	1810 (14)	885 (13)	< .0001
$30,000- $34,999	14718 (19)	6277 (18)	4619 (19)	2574 (20)	1248 (19)	
$35,000- $45,999	21718 (28)	9454 (27)	6705 (28)	3723 (28)	1836 (27)	
$46,000+	27950 (35)	12742 (37)	8414 (35)	4397 (34)	2397 (36)	
Missing	4285 (5)	1982 (6)	1289 (5)	634 (5)	380 (6)	
Comorbidity						
0	37470 (47)	16095 (46)	11671 (48)	6293 (48)	3411 (51)	< .0001
1	28532 (36)	12865 (37)	8532 (35)	4818 (37)	2317 (34)	
2+	12977 (16)	5821 (17)	4111 (17)	2027 (15)	1018 (15)	
Histology						
NOS	224 (0.3)	93 (0.3)	67 (0.3)	45 (0.3)	19 (0.3)	< .0001
Large Cell	3652 (5)	1358 (4)	1225 (5)	695 (5)	374 (6)	
Squamous	22791 (29)	8584 (25)	8069 (33)	4390 (33)	1748 (26)	
Other	4030 (5)	1604 (5)	1254 (5)	781 (6)	391 (6)	
Adenocarcinoma	48282 (61)	23142 (67)	13699 (56)	7227 (55)	4214 (63)	
Tumor Grade						
well/moderately differentiated	46558 (59)	23274 (67)	13619 (56)	6519 (50)	3146 (47)	< .0001

poorly/undifferentiated	29030 (37)	9788 (28)	9699 (40)	6195 (47)	3348 (50)	
Unknown	3391 (4)	1719 (5)	996 (4)	424 (3)	252 (4)	
Tumor Size						
≤3cm	49644 (63)	34452 (99)	6486 (27)	5711 (44)	2995 (44)	< .0001
>3cm-≤5cm	19238 (24)	167 (0.5)	12819 (53)	4188 (32)	2064 (31)	
>5cm	9866 (13)	97 (0.3)	4932 (20)	3175 (24)	1662 (25)	
Unknown	231 (0.3)	65 (0.2)	77 (0.3)	64 (0.5)	25 (0.4)	
Rural/Urban						
Rural	14999 (19)	6312 (18)	4720 (19)	2686 (20)	1281 (19)	< .0001
Urban	59057 (75)	26236 (75)	18097 (74)	9680 (74)	5044 (75)	
Unknown	4923 (6)	2233 (6)	1497 (6)	772 (6)	421 (6)	
Census Region						
Northeast	15939 (20)	7486 (22)	4727 (19)	2374 (18)	1352 (20)	< .0001
Midwest	21583 (27)	9160 (26)	6732 (28)	3787 (29)	1904 (28)	
South	31840 (40)	13980 (40)	9752 (40)	5417 (41)	2691 (40)	
West	9617 (12)	4155 (12)	3103 (13)	1560 (12)	799 (12)	
Primary Site						
C340- Main bronchus	431 (1)	46 (0.1)	95 (0.4)	199 (2)	91 (1)	< .0001
C341-upper lobe	47385 (60)	21947 (63)	13929 (57)	7547 (57)	3962 (59)	
C342-Middle lobe	3819 (5)	1880 (5)	1119 (5)	562 (4)	258 (4)	
C343-Lower lobe	25061 (32)	10323 (30)	8340 (34)	4249 (32)	2149 (32)	
C348-Overlapping lesion	1191 (2)	199 (0.6)	467 (2)	352 (3)	173 (3)	
C349-Lung NOS	1092 (1)	386 (1)	364 (2)	229 (2)	113 (2)	
T category						
T1	40403 (51)	34781 (100)	0 (0)	3716 (28)	1906 (28)	< .0001
T2	33968 (43)	0 (0)	24314 (100)	6360 (48)	3294 (49)	
T3	4608 (6)	0 (0)	0 (0)	3062 (23)	1546 (23)	
N Category						
N0	62157 (79)	34781 (100)	24314 (100)	3062 (23)	0 (0)	< .0001
N1	11108 (14)	0 (0)	0 (0)	10076 (77)	1032 (15)	
N2	5714 (7)	0 (0)	0 (0)	0 (0)	5714 (85)	
Surgery						
Sublobar	7992 (10)	5005 (14)	1797 (7)	599 (5)	591 (9)	< .0001
Lobe/bilobectomy	67209 (85)	29544 (85)	21515 (89)	10907 (83)	5243 (78)	
Pneumonectomy	3778 (5)	232 (1)	1002 (4)	1632 (12)	912 (14)	
Facility type						
Community Cancer Program	5707 (7)	2505 (7)	1746 (7)	1011 (8)	445 (7)	0.0005
Comprehensive Community Cancer Program	37952 (48)	16705 (48)	11724 (48)	6387 (49)	3136 (47)	
Teaching/Research Cancer Program	19304 (24)	8490 (24)	5892 (24)	3162 (24)	1760 (26)	
NCI Program/Network	8954 (11)	4052 (12)	2738 (11)	1395 (11)	769 (11)	
Other	7062 (9)	3029 (9)	2214 (9)	1183 (9)	636 (9)	

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Supplemental Table IIB. Patient Demographic and Institutional Characteristics Among Margin Negative Patients by Adjuvant Therapy.

Categories	Total	No Treatment	Chemotherapy	Radiation therapy	Chemoradiation	p-value
	N=78979 N (%)	N=61281 N (%)	N=13665 N (%)	N=988 N (%)	N=3045 N (%)	
Stage Group						
Stage IA	34781 (44)	33780 (55)	789 (6)	136 (14)	76 (3)	< .0001
Stage IB & IIA	24314 (31)	19281 (32)	4568 (33)	250 (25)	215 (7)	
Stage IIA & IIB	13138 (17)	6101 (10)	5788 (42)	354 (36)	895 (29)	
Stage IIIA	6746 (9)	2119 (4)	2520 (18)	248 (25)	1859 (61)	
Age Group						
18-49	4389 (6)	2882 (5)	1114 (8)	56 (6)	337 (11)	< .0001
50-64	25864 (33)	18296 (30)	5962 (44)	261 (26)	1345 (44)	
65-74	29782 (38)	23397 (38)	4981 (37)	382 (39)	1022 (34)	
75-90	18944 (24)	16706 (27)	1608 (12)	289 (29)	341 (11)	
Sex						
Male	37844 (48)	28854 (47)	6856 (50)	547 (55)	1587 (52)	< .0001
Female	41135 (52)	32427 (53)	6809 (50)	441 (45)	1458 (48)	
Race/Ethnicity						
Non-Hispanic, White	61957 (79)	48361 (79)	10515 (77)	758 (77)	2323 (76)	< .0001
Hispanic	1734 (2)	1356 (2)	297 (2)	17 (2)	64 (2)	
Black	6478 (8)	4803 (8)	1293 (10)	96 (10)	286 (9)	
Other	2078 (3)	1616 (3)	346 (3)	28 (3)	88 (3)	
Missing	6732 (9)	5145 (8)	1214 (9)	89 (9)	284 (9)	
Insurance						
Uninsured	1517 (2)	1091 (2)	341 (3)	16 (2)	69 (2)	< .0001
Medicaid	3325 (4)	2382 (4)	720 (5)	51 (5)	172 (6)	
Younger Medicare	4538 (6)	3413 (6)	849 (6)	59 (6)	217 (7)	
Older Medicare	41134 (52)	33907 (55)	5528 (41)	576 (58)	1123 (37)	
Private	27402 (35)	19609 (32)	6083 (45)	277 (28)	1433 (47)	

Missing	1063 (1)	879 (1)	144 (1)	9 (1)	31 (1)	
Median Income-Quartile						
<$30,000	10308 (13)	7968 (13)	1808 (13)	158 (16)	374 (12)	< .0001
$30,000- $34,999	14718 (19)	11386 (19)	2498 (18)	221 (22)	613 (20)	
$35,000- $45,999	21718 (28)	16705 (27)	3878 (28)	270 (27)	865 (28)	
$46,000+	27950 (35)	21822 (36)	4807 (35)	300 (30)	1021 (34)	
Missing	4285 (5)	3400 (6)	674 (5)	39 (4)	172 (6)	
Comorbidity						
0	37470 (47)	28612 (47)	6848 (50)	438 (44)	1572 (52)	< .0001
1	28532 (36)	22149 (36)	4945 (36)	364 (37)	1074 (35)	
2+	12977 (16)	10520 (17)	1872 (14)	186 (19)	399 (13)	
Histology						
NOS	224 (0.3)	175 (0.3)	36 (0.3)	2 (0.2)	11 (0.4)	< .0001
Large Cell	3652 (5)	2581 (4)	821 (6)	64 (7)	186 (6)	
Squamous	22791 (29)	17710 (29)	3897 (29)	383 (39)	801 (26)	
Other	4030 (5)	3031 (5)	739 (5)	62 (6)	198 (7)	
Adenocarcinoma	48282 (61)	37784 (62)	8172 (60)	477 (48)	1849 (61)	
Tumor Grade						
well/moderately differentiated	46558 (59)	37923 (62)	6827 (50)	496 (50)	1312 (43)	< .0001
poorly/undifferentiated	29030 (37)	20626 (34)	6356 (47)	449 (46)	1599 (53)	
Unknown	3391 (4)	2732 (5)	482 (4)	43 (4)	134 (4)	
Tumor Size						
≤3cm	49644 (63)	42437 (69)	5367 (39)	448 (45)	1392 (46)	< .0001
>3cm-≤5cm	19238 (24)	13070 (21)	4923 (36)	324 (33)	921 (30)	
>5cm	9866 (13)	5600 (9)	3335 (24)	210 (21)	721 (24)	
Unknown	231 (0.3)	174 (0.3)	40 (0.3)	6 (0.6)	11 (0.4)	
Rural/Urban						
Rural	14999 (19)	11672 (19)	2540 (19)	196 (20)	591 (19)	0.034
Urban	59057 (75)	45716 (75)	10335 (76)	746 (76)	2260 (74)	
Unknown	4923 (6)	3893 (6)	790 (6)	46 (5)	194 (6)	
Census Region						
Northeast	15939 (20)	12446 (20)	2734 (20)	161 (16)	598 (20)	< .0001
Midwest	21583 (27)	15988 (26)	4355 (32)	268 (27)	972 (32)	

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South	31840 (40)	24965 (41)	5215 (38)	432 (44)	1228 (40)	
West	9617 (12)	7882 (13)	1361 (10)	127 (13)	247 (8)	
Primary Site						
C340- Main bronchus	431 (1)	250 (0.4)	152 (1)	6 (1)	23 (1)	< .0001
C341-upper lobe	47385 (60)	36984 (60)	7838 (57)	626 (63)	1937 (64)	
C342-Middle lobe	3819 (5)	3024 (5)	617 (5)	40 (4)	138 (5)	
C343-Lower lobe	25061 (32)	19451 (32)	4509 (33)	278 (28)	823 (27)	
C348-Overlapping lesion	1191 (2)	768 (1)	333 (2)	19 (2)	71 (2)	
C349-Lung NOS	1092 (1)	804 (1)	216 (2)	19 (2)	53 (2)	
T category						
T1	40403 (51)	35961 (59)	3285 (24)	261 (26)	896 (29)	< .0001
T2	33968 (43)	23130 (38)	8800 (64)	494 (50)	1544 (51)	
T3	4608 (6)	2190 (4)	1580 (12)	233 (24)	605 (20)	
N Category						
N0	62157 (79)	54703 (89)	6292 (46)	565 (57)	597 (20)	< .0001
N1	11108 (14)	4855 (8)	5317 (39)	210 (21)	726 (24)	
N2	5714 (7)	1723 (3)	2056 (15)	213 (22)	1722 (57)	
Surgery						
Sublobar	7992 (10)	6738 (11)	718 (5)	169 (17)	367 (12)	< .0001
Lobe/bilobectomy	67209 (85)	52526 (86)	11513 (84)	744 (75)	2426 (80)	
Pneumonectomy	3778 (5)	2017 (3)	1434 (11)	75 (8)	252 (8)	
Facility type						
Community Cancer Program	5707 (7)	4283 (7)	1023 (8)	112 (11)	289 (10)	< .0001
Comprehensive Community Cancer Program	37952 (48)	29420 (48)	6456 (47)	500 (51)	1576 (52)	
Teaching/Research Cancer Program	19304 (24)	15141 (25)	3235 (24)	214 (22)	714 (24)	
NCI Program/Network	8954 (11)	7039 (12)	1657 (12)	67 (7)	191 (6)	
Other	7062 (9)	5398 (9)	1294 (10)	95 (10)	275 (9)	

Supplemental Table III. Propensity Score Adjusted Models

		Margin Positive			Margin Negative		
	Post-Op Treatment	**N**	**Propensity Adjusted Hazard Ratio (95% CI)**	**P-Value**	**N**	**Propensity Adjusted Hazard Ratio (95% CI)**	**P-Value**
Group 1: Stage IA (T1ab, N0)	No Treatment	265	1.00 (Referent)		33780	1.00 (Referent)	
	Chemo Only	19	0.94 (0.36-2.44)	0.8968	789	1.02 (0.87-1.20)	0.7841
	Radiation Only	60	1.87 (1.16-3.04)	0.011	136	2.37 (1.81-3.09)	<.0001
	Chemo + Rad	25	1.39 (0.73-2.63)	0.3142	76	2.91 (2.02-4.19)	<.0001
Group 2: Stage IB (T2a, N0) & Stage IIA (T2b, N0)	No Treatment	477	1.00 (Referent)		19281	1.00 (Referent)	
	Chemo Only	142	0.58 (0.40-0.83)	0.0032	4568	0.73 (0.68-0.78)	<.0001
	Radiation Only	119	1.30 (0.97-1.73)	0.0818	250	1.79 (1.49-2.16)	<.0001
	Chemo + Rad	119	1.01 (0.73-1.39)	0.9688	215	1.42 (1.15-1.76)	0.0012
Group 3: Stage IIA (T1ab-T2a, N1) & Stage IIB (T3, N0;T2b N1)	No Treatment	419	1.00 (Referent)		6101	1.00 (Referent)	
	Chemo Only	284	0.73 (0.59-0.91)	0.0058	5788	0.66 (0.62-0.71)	<.0001
	Radiation Only	199	1.02 (0.81-1.28)	0.8649	354	1.37 (1.19-1.59)	<.0001
	Chemo + Rad	415	0.78 (0.64-0.97)	0.0218	895	1.05 (0.95-1.18)	0.341
	Chemo+Rad	146	0.81 (0.61-1.07)	0.1343	431	1.04 (0.89-1.20)	0.6584
	Rad+Chemo	120	0.77 (0.57-1.06)	0.1054	224	1.12 (0.93-1.37)	0.24
	Chemo=Rad	149	0.80 (0.59-1.07)	0.1344	240	1.06 (0.86-1.29)	0.5967
Group 4: Stage IIIA (T1-3, N2; T3, N1)	No Treatment	245	1.00 (Referent)		2119	1.00 (Referent)	
	Chemo Only	200	0.74 (0.58-0.95)	0.0167	2520	0.64 (0.58-0.69)	<.0001
	Radiation Only	69	1.13 (0.83-1.54)	0.4428	248	1.17 (0.98-1.38)	0.0757
	Chemo + Rad	404	0.67 (0.54-0.83)	0.0003	1859	0.71 (0.65-0.79)	<.0001
	Chemo+Rad	173	0.59 (0.45-0.77)	0.0001	1096	0.64 (0.56-0.71)	<.0001
	Rad+Chemo	96	0.79 (0.57-1.09)	0.1434	316	0.77 (0.65-0.92)	0.0038
	Chemo=Rad	135	0.59 (0.44-0.80)	0.0006	447	0.78 (0.67-0.90)	0.001

Supplemental Table IV. Proportional Hazards Models by Stage Group and Margin Status After removal of exposure groups where the Proportional Hazards assumption is questionable.

		Margin Positive			
	Post-Op Treatment	**N**	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**	**P-Value**
Group 1: Stage	No Treatment	265	1.00 (Referent)	1.00 (Referent)	

IA (T1ab, N0)	Chemo Only (patients who had chemotherapy only were excluded from the analysis)				
	Radiation Only	60	**1.98 (1.25-3.12)**	**1.75 (1.03-2.97)**	0.0385
	Chemo + Rad	25	1.69 (0.92-3.11)	0.92 (0.44-1.92)	0.8202
Group 3: Stage IIA (T1ab-T2a, N1) & Stage IIB (T3, N0;T2b N1)	No Treatment	419	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	284	**0.65 (0.53-0.81)**	**0.72 (0.58-0.90)**	0.0042
	Radiation Only (patients who had radiation therapy only were excluded from the analysis)				
	Chemo + Rad	415	**0.68 (0.56-0.83)**	**0.77 (0.63-0.95)**	0.0148

Supplemental Table V. Kaplan Meier Survival Analysis and Proportional Hazards Models by Stage Group for Margin Positive Patients Evaluating the Order of Chemotherapy and Radiation

		Margin Positive				
	Post-Op Treatment	**N**	**5 Year Overall Survival (log-rank p-Value)**	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**	**P-Value**
Group 3: Stage IIA (T1ab-T2a, N1) & Stage IIB (T3, N0;T2b N1)	No Treatment	419	27 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	284	36 (0.0001)	0.65 (0.53-0.81)	0.72 (0.58-0.9)	0.0041
	Radiation Only	199	26 (0.5907)	1.06 (0.85-1.32)	0.94 (0.74-1.18)	0.5878
	Chemo + Rad	415	37 (<.0001)	0.68 (0.56-0.83)	0.76 (0.62-0.93)	0.0083
	Chemo+Rad	146	37 (0.0106)	0.70 (0.54-0.92)	0.74 (0.56-0.98)	0.034
	Rad+Chemo	120	36 (0.0136)	0.69 (0.52-0.92)	0.76 (0.56-1.02)	0.071
	Chemo=Rad	149	38 (0.0036)	0.66 (0.50-0.87)	0.79 (0.59-1.06)	0.1099
Group 4: Stage IIIA (T1-3, N2; T3, N1)	No Treatment	245	12 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	200	21 (0.0048)	0.70 (0.55-0.90)	0.77 (0.6-1)	0.0466
	Radiation Only	69	10 (0.5215)	1.11 (0.81-1.51)	1.03 (0.74-1.43)	0.8729
	Chemo + Rad	404	25 (<.0001)	0.59 (0.48-0.72)	0.63 (0.51-0.79)	<.0001
	Chemo+Rad	173	28 (<.0001)	0.54 (0.42-0.70)	0.56 (0.43-0.74)	<.0001
	Rad+Chemo	96	19 (0.0275)	0.70 (0.52-0.95)	0.79 (0.57-1.09)	0.1508
	Chemo=Rad	135	24 (0.0002)	0.58 (0.44-0.77)	0.63 (0.46-0.84)	0.0021

Supplemental Table VI. Survival results for Margin Positive Patients by R1, R2, and R-Unknown

Margin Status	**Post-Op Treatment**	**Stage IIA (T1ab-T2a, N1) & Stage IIB (T3, N0;T2b N1) Margin Positive (N=1327)**			**Stage IIIA (T1-3, N2; T3, N1) Margin Positive (N=919)**		
		Total N	**5 Year Overall Survival (log-rank p-**	**Adjusted Hazard Ratio (95% CI) P-Value**	**Total N**	**5 Year Overall Survival (log-rank**	**Adjusted Hazard Ratio (95% CI) P-Value**

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			value)**				p-value)**		
R1	No Treatment	231	26 (referent)	1.00 (Referent)		127	15 (referent)	1.00 (Referent)	
	Chemo Only	146	36 (0.0024)	0.65(0.47-0.88)	0.0063	121	19 (0.1362)	0.83(0.59-1.17)	0.2876
	Radiation Only	135	29 (0.5925)	0.83(0.61-1.13)	0.2376	29	13 (0.9215)	0.97(0.57-1.62)	0.8925
	Chemo + Rad	241	37 (0.0019)	0.66(0.5-0.87)	0.0036	237	23 (0.001)	**0.66(0.48-0.91)**	**0.0101**
R2	No Treatment	13	23 (referent)	ID*		14	32 (referent)	ID*	
	Chemo Only	12	48 (0.0833)	ID*		5	40 (0.9666)	ID*	
	Radiation Only	6	0 (0.6098)	ID*		6	17 (0.5783)	ID*	
	Chemo + Rad	22	35 (0.1247)	ID*		18	9 (06722)	ID*	
RX	No Treatment	178	31 (referent)	1.00 (Referent)		105	8 (referent)	1.00 (Referent)	
	Chemo Only	129	35 (0.0503)	0.78(0.55-1.11)	0.1703	78	25 (0.0075)	**0.6(0.38-0.95)**	**0.0284**
	Radiation Only	61	23 (0.1165)	1.16(0.76-1.76)	0.4983	35	8 (0.7908)	1.13(0.67-1.91)	0.6458
	Chemo + Rad	153	37 (0.0649)	1.1(0.77-1.57)	0.6078	144	30 (<.0001)	**0.48(0.33-0.69)**	**<.0001**

*ID= Insufficient Data **P-value from the log-rank test, comparing the entire survival curves.

Supplemental Table VII. Analysis of Stage Group 4, Margin negative patients by pN stage (N0/N1 vs. N2)

		Stage Group IV: Stage IIIA (T1-3, N2; T3, N1) Margin Negative Patients Only (R0)				
pN Stage	**Post-Op Treatment**	**N**	**5 Year Overall Survival (log-rank p-value)****	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**	**Propensity Adjusted Hazard Ratio (95% CI)**
N0,N1	No Treatment	396	27 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)

	Chemo Only	464	46 (<.0001)	0.46 (0.37-0.57)	0.49 (0.39-0.62)	2.54 (1.30-4.95)
	Radiation Only	35	28 (0.6906)	1.10 (0.71-1.70)	0.94 (0.59-1.48)	1.08 (0.69-1.69)
	Chemo + Rad	137	23 (0.2422)	0.85 (0.65-1.10)	0.89 (0.67-1.18)	0.92 (0.70-1.21)
	Chemo+Rad	74	23 (0.1490)	0.77 (0.54-1.09)	0.85 (0.59-1.21)	0.84 (0.59-1.19)
	Rad+Chemo	36	12 (0.5019)	1.28 (0.79-2.08)	1.28 (0.77-2.13)	1.11 (0.67-1.84)
	Chemo=Rad	27	29 (0.3696)	0.75 (0.47-1.22)	0.73 (0.44-1.23)	0.96 (0.58-1.59)
	No Treatment	1723	23 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
	Chemo Only	2056	38 (<.0001)	0.62 (0.56-0.68)	0.65 (0.59-0.71)	0.65 (0.59-0.72)
	Radiation Only	213	15 (0.0620)	1.20 (1-1.44)	1.18 (0.98-1.42)	1.19 (0.99-1.43)
N2	Chemo + Rad	1722	40 (<.0001)	0.61 (0.56-0.68)	0.67 (0.60-0.74)	0.69 (0.62-0.76)
	Chemo+Rad	1022	43 (<.0001)	0.55 (0.49-0.62)	0.61 (0.54-0.69)	0.61 (0.54-0.69)
	Rad+Chemo	280	36 (0.0002)	0.70 (0.59-0.84)	0.74 (0.61-0.89)	0.74 (0.62-0.90)
	Chemo=Rad	420	34 (<.0001)	0.72 (0.62-0.84)	0.77 (0.66-0.91)	0.77 (0.66-0.91)

Supplemental Table VIII. Kaplan Meier Survival Analysis and Proportional Hazards Models by Stage Group for Margin Negative Patients Evaluating the Order of Chemotherapy and Radiation.

		Margin Negative				
	Post-Op Treatment	**N**	**5 Year Overall Survival (log-rank p-Value)**	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**	**P-Value**
Group	No Treatment	33780	72 (Referent)	1.00 (Referent)	1.00 (Referent)	

1: Stage IA (T1ab, N0)	Chemo Only	789	74 (0.2946)	0.92 (0.78-1.08)	1.02 (0.87-1.2)	0.816
	Radiation Only	136	44 (<.0001)	2.89 (2.22-3.73)	2.18 (1.67-2.85)	<.0001
	Chemo + Rad	76	40 (<.0001)	3.19 (2.21-4.59)	2.99 (2.07-4.31)	<.0001
Group 2: Stage IB (T2a, N0) & Stage IIA (T2b, N0)	No Treatment	19281	57 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	4568	68 (<.0001)	0.68 (0.63-0.72)	0.74 (0.69-0.8)	<.0001
	Radiation Only	250	38 (<.0001)	1.92 (1.60-2.31)	1.8 (1.49-2.16)	<.0001
	Chemo + Rad	215	47 (0.0003)	1.47 (1.19-1.81)	1.41 (1.14-1.74)	0.0016
Group 3: Stage IIA (T1ab-T2a, N1) & Stage IIB (T3, N0;T2b N1)	No Treatment	6101	37 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	5788	53 (<.0001)	0.59 (0.56-0.63)	0.66 (0.62-0.7)	<.0001
	Radiation Only	354	28 (<.0001)	1.35 (1.17-1.57)	1.36 (1.18-1.58)	<.0001
	Chemo + Rad	895	41 (0.1772)	0.93 (0.84-1.03)	1.04 (0.93-1.16)	0.4811
	Chemo+Rad	431	42 (0.1966)	0.91 (0.78-1.05)	1 (0.86-1.16)	0.978
	Rad+Chemo	224	36 (0.9445)	0.99 (0.82-1.20)	1.13 (0.93-1.37)	0.209
	Chemo=Rad	240	42 (0.3621)	0.91 (0.75-1.11)	1.03 (0.84-1.26)	0.782
Group 4: Stage IIIA (T1-3, N2; T3, N1)	No Treatment	2119	24 (Referent)	1.00 (Referent)	1.00 (Referent)	
	Chemo Only	2520	39 (<.0001)	0.59 (0.55-0.65)	0.63 (0.58-0.69)	<.0001
	Radiation Only	248	18 (0.0747)	1.18 (0.99-1.39)	1.15 (0.97-1.37)	0.1025
	Chemo + Rad	1859	39 (<.0001)	0.62 (0.57-0.68)	0.69 (0.63-0.76)	<.0001
	Chemo+Rad	1096	42 (<.0001)	0.56 (0.50-0.62)	0.62 (0.56-0.7)	<.0001
	Rad+Chemo	316	34 (0.0006)	0.74 (0.62-0.87)	0.79 (0.66-0.94)	0.0064
	Chemo=Rad	447	34 (<.0001)	0.72 (0.62-0.83)	0.77 (0.67-0.9)	0.0006

Supplemental Table IX. Analysis including only Anatomic Resections

		Margin Positive		
	Post-Op Treatment	**N**	**Adjusted Hazard Ratio (95% CI)**	**P-Value**
Group 1: Stage IA (T1ab, N0)	No Treatment	197	1.00 (Referent)	
	Chemo Only	13	0.86 (0.18-4.16)	0.8501
	Radiation Only	31	4.14 (1.88-9.09)	0.0004
	Chemo + Rad	14	1.14 (0.38-3.44)	0.8125

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Group 2: Stage IB (T2a, N0) & Stage IIA (T2b, N0)	No Treatment	423	1.00 (Referent)	
	Chemo Only	131	0.54 (0.37-0.80)	0.0023
	Radiation Only	100	1.33 (0.96-1.85)	0.0899
	Chemo + Rad	108	0.94 (0.66-1.32)	0.7036
Group 3: Stage IIA (T1ab-T2a, N1) & Stage IIB (T3, N0;T2b N1)	No Treatment	386	1.00 (Referent)	
	Chemo Only	266	0.75 (0.60-0.95)	0.016
	Radiation Only	177	0.99 (0.77-1.27)	0.9379
	Chemo + Rad	379	0.80 (0.64-0.99)	0.0389
Group 4: Stage IIIA (T1-3, N2; T3, N1)	No Treatment	220	1.00 (Referent)	
	Chemo Only	179	0.73 (0.56-0.96)	0.0229
	Radiation Only	61	1.05 (0.74-1.48)	0.7959
	Chemo + Rad	356	0.66 (0.53-0.84)	0.0006

Supplemental Table X. Numbers of Events in Each Analysis Group

		Margin Positive		**Margin Negative**	
	Post-Op Treatment	**N**	**Event=death**	**N**	**Event=death**
Group 1: Stage IA (T1ab, N0)	No Treatment	265	75 (28.3)	33780	5695 (16.86)
	Chemo Only	19	6 (31.58)	789	157 (19.9)
	Radiation Only	60	25 (41.67)	136	55 (40.44)
	Chemo + Rad	25	12 (48)	76	29 (28.16)
Group 2: Stage IB (T2a, N0) & Stage IIA (T2b, N0)	No Treatment	477	182 (38.16)	19281	5427 (28.15)
	Chemo Only	142	39 (27.46)	4568	996 (21.8)
	Radiation Only	119	62 (52.1)	250	114 (45.6)
	Chemo + Rad	119	53 (44.54)	215	88 (40.93)
Group 3: Stage IIA	No Treatment	419	239 (57.04)	6101	2663 (43.65)

(T1ab-T2a, N1) & Stage IIB (T3, N0;T2b N1)	Chemo Only	284	129 (45.42)	5788	1691 (29.22)
	Radiation Only	199	121 (60.8)	354	198 (55.93)
	Chemo + Rad	415	186 (44.82)	895	398 (44.47)
	Chemo+Rad	146	69 (47.26)	431	186 (43.16)
	Rad+Chemo	120	56 (46.67)	224	109 (48.66)
	Chemo=Rad	149	61 (40.94)	240	103 (42.92)
Group 4: Stage IIIA (T1-3, N2; T3, N1)	No Treatment	245	170 (69.39)	2119	1218 (57.48)
	Chemo Only	200	107 (53.5)	2520	969 (38.45)
	Radiation Only	69	53 (76.81)	248	151 (60.89)
	Chemo + Rad	404	213 (52.72)	1859	791 (42.55)
	Chemo+Rad	173	90 (52.02)	1096	426 (38.87)
	Rad+Chemo	96	54 (56.25)	316	150 (47.47)
	Chemo=Rad	135	69 (51.11)	447	215 (48.1)

Supplemental Figure I. Consort Diagram for Margin Negative

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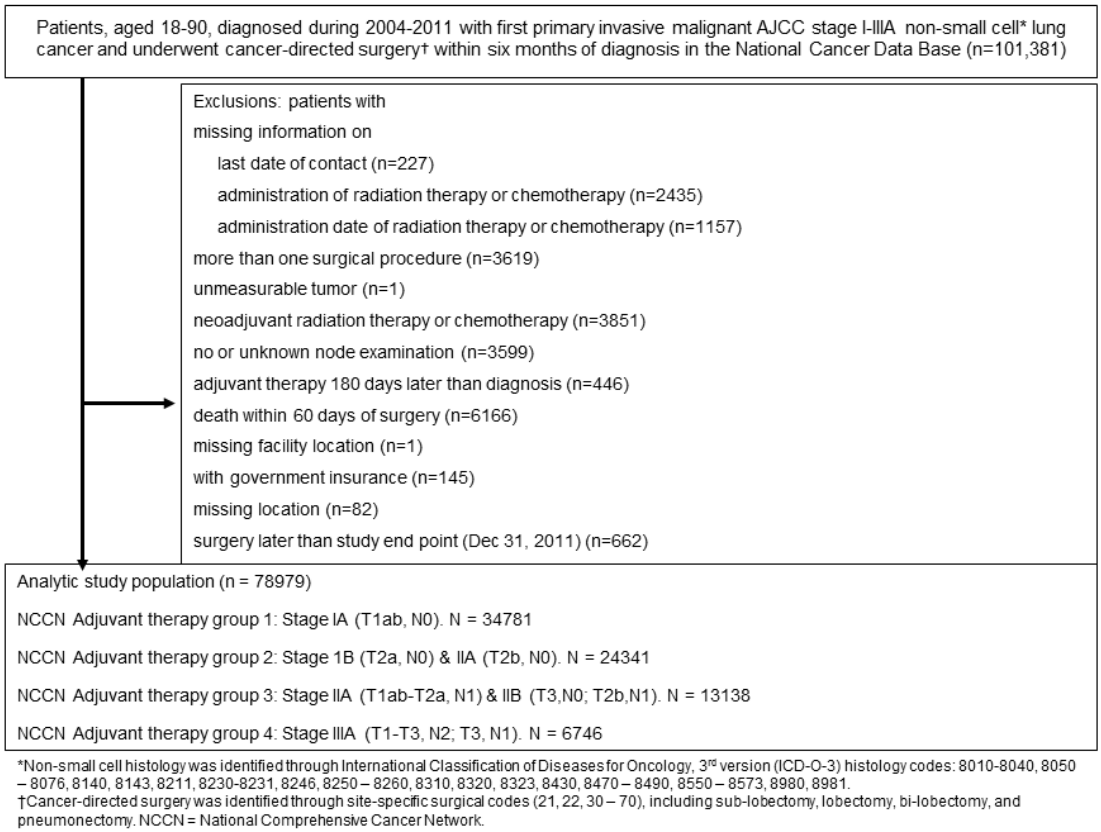
Supplemental Figure I: Patient selection schema among margin-negative NSCLC patients



*Non-small cell histology was identified through International Classification of Diseases for Oncology, 3rd version (ICD-O-3) histology codes: 8010-8040, 8050 – 8076, 8140, 8143, 8211, 8230-8231, 8246, 8250 – 8260, 8310, 8320, 8323, 8430, 8470 – 8490, 8550 – 8573, 8980, 8981.
†Cancer-directed surgery was identified through site-specific surgical codes (21, 22, 30 – 70), including sub-lobectomy, lobectomy, bi-lobectomy, and pneumonectomy. NCCN = National Comprehensive Cancer Network.

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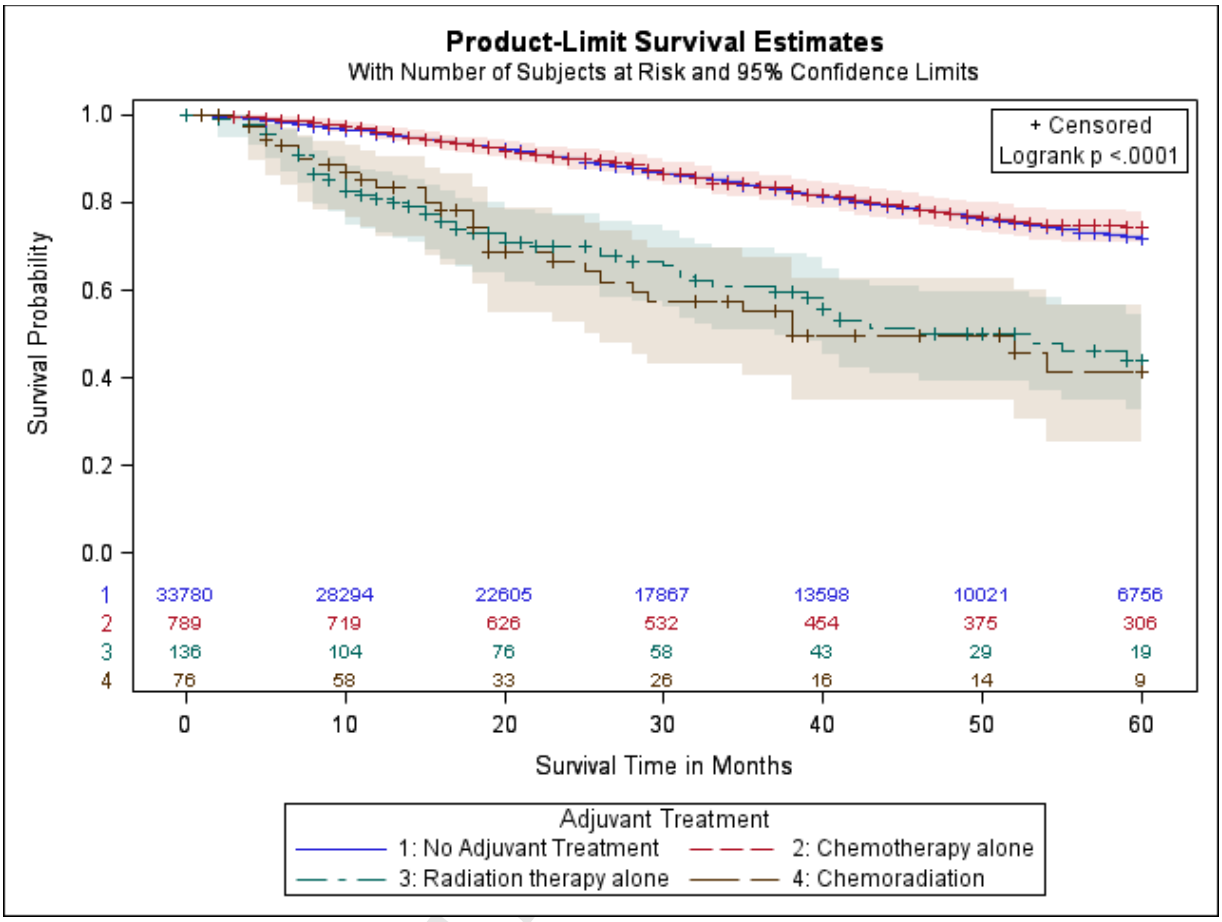
Figure S-II. Kaplan Meier Survival Curves for Margin Negative Patients by Stage Group

IIA. Group 1



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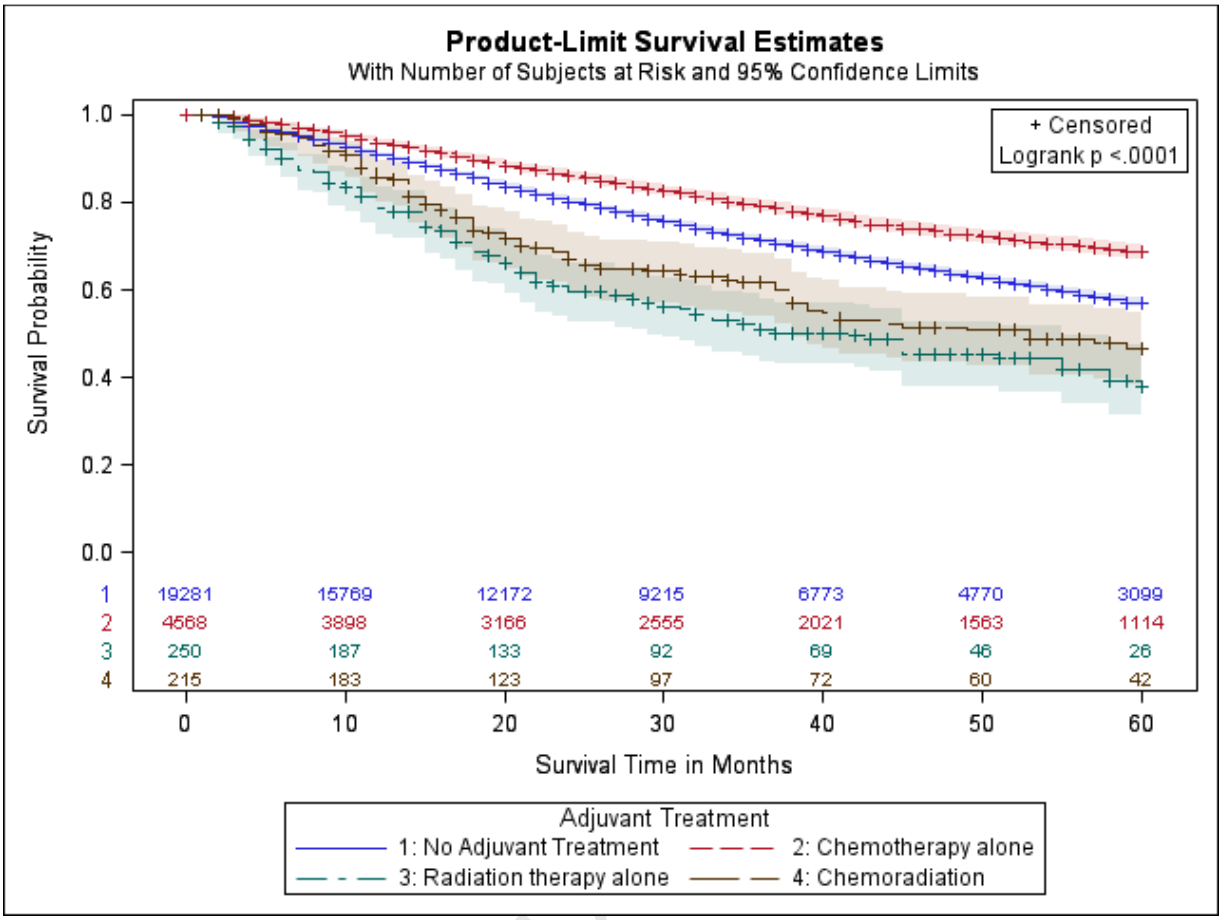
IIB. Group 2



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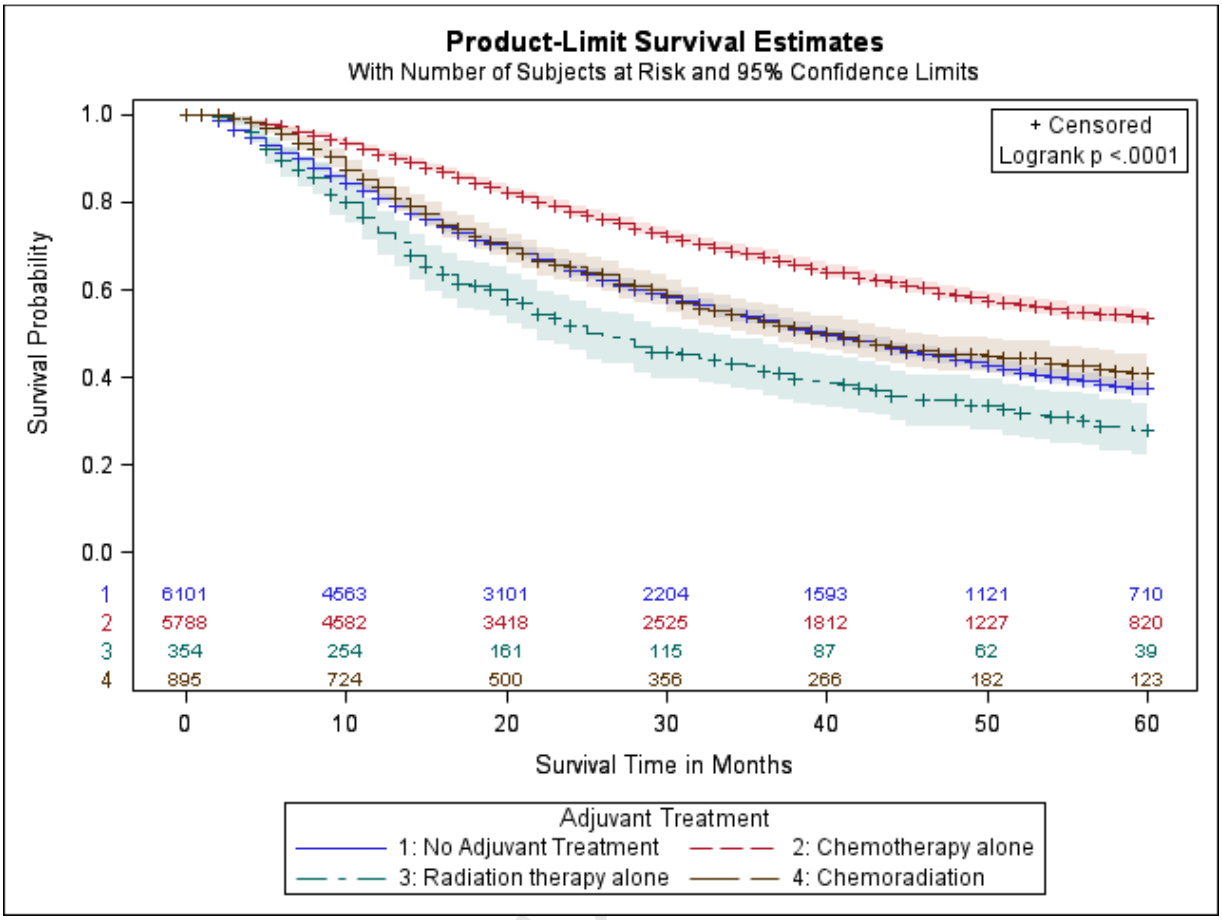
IIC. Group 3



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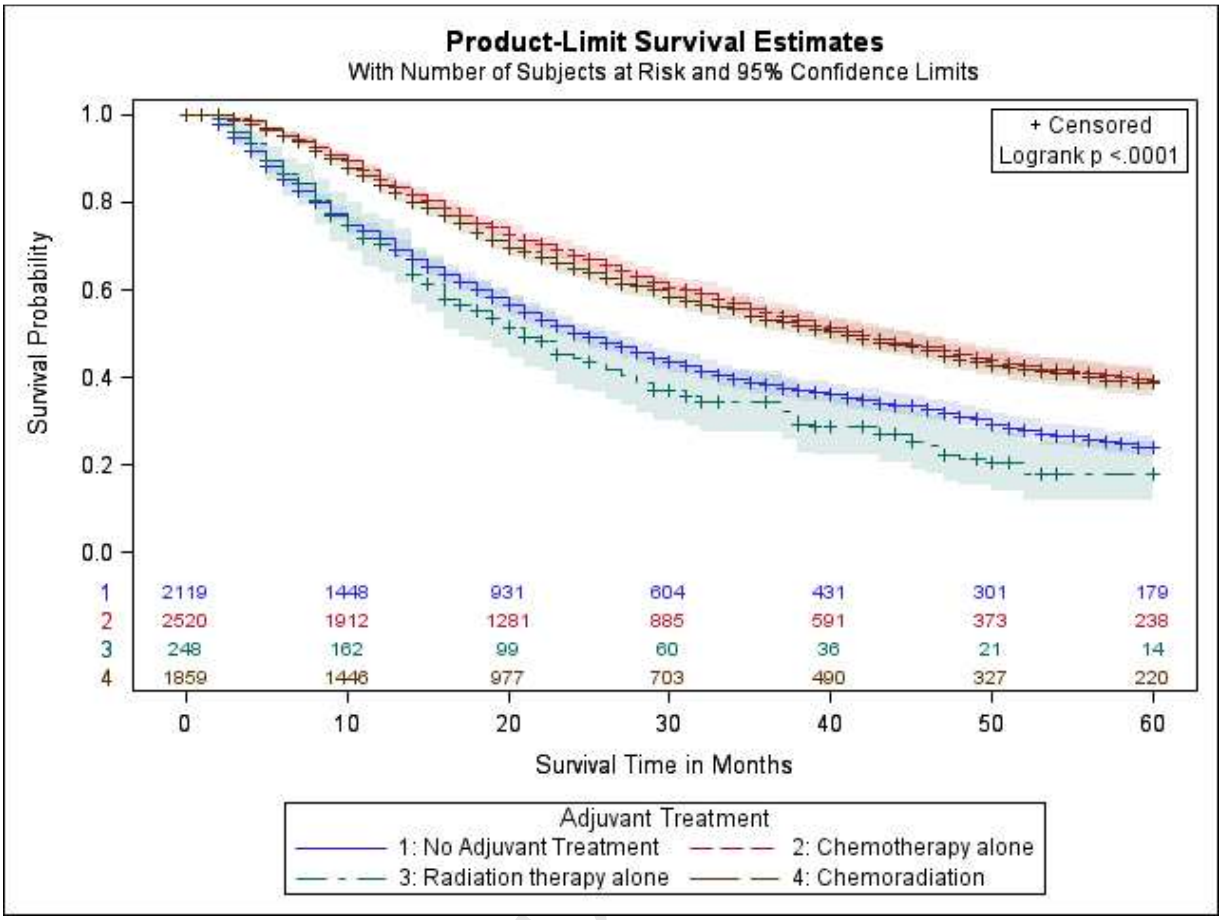
IID. Group 4


Product-Limit Survival Estimates
With Number of Subjects at Risk and 95% Confidence Limits
+ Censored
Logrank p <.0001
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
1 2119 1448 931 604 431 301 179
2 2520 1912 1281 885 591 373 238
3 248 162 99 60 36 21 14
4 1859 1446 977 703 490 327 220
0 10 20 30 40 50 60
Survival Time in Months
Adjuvant Treatment
1: No Adjuvant Treatment
2: Chemotherapy alone
3: Radiation therapy alone
4: Chemoradiation

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