Adhering to guideline concordant care improves survival among the different subtypes of T3 N2 non–small cell lung cancer

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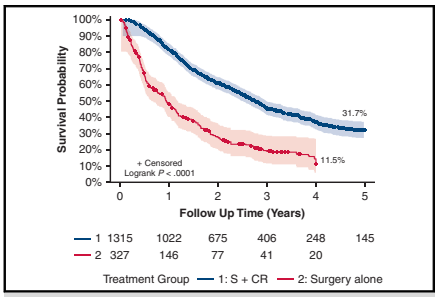
ABSTRACT

Objectives: T3 disease comprises heterogeneous morphologic characteristics, a variation only further complicated when in the context of N2-confirmed involvement. This study aims to examine whether or not specific features of T3 N2 non–small cell lung cancer are associated with improved 5-year overall survival when using a multimodal therapeutic approach consistent with guideline recommendations compared with definitive surgery alone.

Methods: Patients with pathologic T3 N2 non–small cell lung cancer were identified in the National Cancer Database. Therapy modality, as defined by surgery alone versus surgery with adjuvant therapy, and T3 disease descriptors were compared for differences in 5-year overall survival using Kaplan-Meier analysis and log-rank tests. Multivariable Cox regression was used to determine prognostic factors for survival.

Results: A total of 1924 patients met the inclusion criteria. Of these, 80.0% (n = 1539) received adjuvant chemotherapy with or without radiation therapy following surgery and 20.0% (n = 385) underwent definitive surgery alone. Patients in the 2 cohorts differed significantly in age, race, insurance status, and Charlson-Deyo score ($P < .05$). The overall survival for patients who underwent surgery followed by chemotherapy with or without radiation therapy compared with those who underwent surgery alone was 31.7% and 11.1%, respectively ($P < .0001$). Multivariable analysis demonstrated a lower risk of death with multimodal therapeutic intervention compared with surgery alone for patients with disease marked by chest wall invasion, additional ipsilateral pulmonary nodules, tumor size, and the presence of multiple T3 features.

Conclusions: The utilization of a multimodal approach to treating pathologic T3 N2 NSCLC, compared with surgery alone, is associated with superior overall survival and lower risk of death for many subtypes of T3 disease. (JTCVS Open 2022;10:384-92)



Multimodal therapy is associated with higher survival versus surgery alone in T3 N2 disease.

CENTRAL MESSAGE

T3 N2 NSCLC treated with surgery followed by adjuvant therapy is associated with improved survival compared with surgery alone, irrespective of T3 descriptor heterogeneity.

PERSPECTIVE

Clinical guidelines offer multiple approaches to T3 N2 NSCLC disease. This study demonstrates that a multimodal approach inclusive of surgery, compared with surgery alone, is associated with improved overall survival and a lower risk of death in T3 N2 disease, even in the context of heterogeneous T3 descriptors.

See Commentary on page 393.

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Abbreviations and Acronyms

ADN = additional nodules in the ipsilateral lung, same lobe
AJCC = American Joint Committee on Cancer
CWI = chest wall invasion or resection
GCC = guideline-concordant care
NCDB = National Cancer Database
NSCLC = non–small cell lung cancer
S = surgery alone
S + CR = surgery followed by chemotherapy with or without radiation therapy
TSZ = tumor size >5 and ≤7 cm

▶ Video clip is available online.

Clinical practice guidelines represent an integration of evidence based on clinical trials and studies deemed to be of high quality as well as expert professional opinion. They help clinicians and patients work through the shared decision-making process associated with delivering personalized care. In doing so, the use of evidence-based guidelines also has been associated with improving outcomes and controlling health care costs.[1] In the context of lung cancer, it has been demonstrated that patients with lung cancer who receive guideline-concordant care (GCC) have a survival advantage compared with those who do not receive GCC.[2,3]

With regard to non–small cell lung cancer (NSCLC) disease, T3 disease encompasses a diverse set of lesion morphology. In the eighth edition staging system, presentations with tumor size >5 and ≤7 cm; with chest wall, phrenic nerve, or parietal pericardium invasion; or with additional nodules in the ipsilateral lung of the same lobe all qualified as being a T3 descriptor.[4] When presenting simultaneously, the different possible permutations of T3 descriptors following surgical resection presents challenging clinical management scenarios, particularly when in the context of N2 disease, for which the clinician may need to be prepared to take into consideration when counseling patients.

Per the National Comprehensive Cancer Network, the recommended treatment for T3 N2 patients following definitive surgery with negative margins is to receive adjuvant or sequential chemotherapy with radiation therapy.[5] However, the relationship of GCC and survival advantage has not been observed consistently in Stage III-N2 disease, likely owing to its aforementioned heterogeneous presentation.[6] When compounded with the heterogeneous phenotype of T3 disease, an important clinical question emerges regarding whether or not guideline recommendations confer equal survival advantages across the various permutations of T3 N2 presentation. Currently, a gap in knowledge exists regarding whether or not the different T3 descriptors influence outcomes associated with surgically resected N2 disease.

Therefore, the primary objective of this study is to examine outcomes on the basis of different T3 descriptors

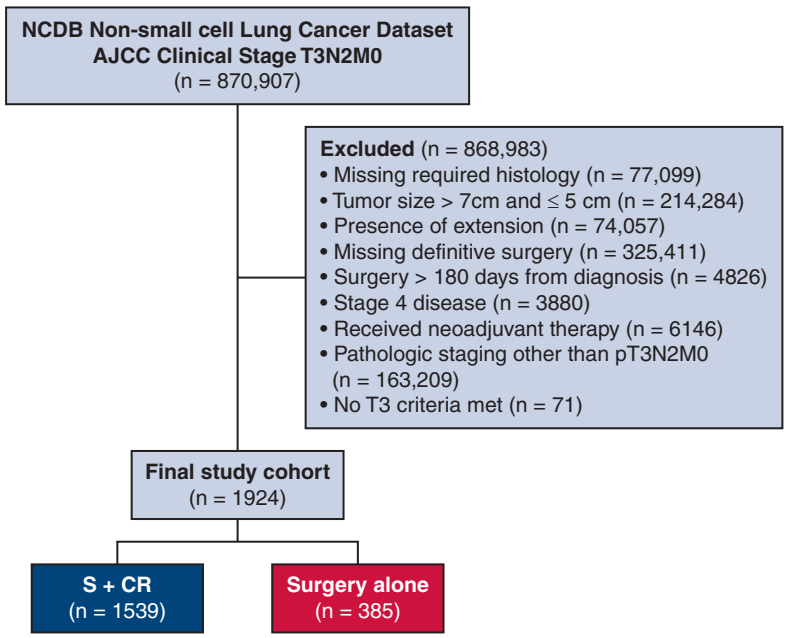


FIGURE 1. Consolidated Standards of Reporting Trials diagram. Cohort of patients with pathologic T3 N2 M0 non–small cell lung cancer (NSCLC) from the National Cancer Database (*NCDB*). *AJCC*, American Joint Committee on Cancer; *S + CR*, surgery followed by chemotherapy with or without radiation.

TABLE 1. Demographic and clinical characteristics of patients with T3 N2 non–small cell lung cancer (NSCLC) disease

Characteristic	S + CR		S		*P* value
Age (y)	66.5 ± 9.6		66.5 ± 9.6		
Sex					.02
Female	754	49.0	164	42.6	
Male	785	51.0	221	57.4	
Race					.005
Missing	12	0.78	–*	–*	
Black	152	9.9	20	5.2	
Other	48	3.1	–*	–*	
White	1327	86.2	354	92.0	
Insurance					< .0001
Missing	26	1.7	–*	–*	
Medicaid	102	6.6	16	4.2	
Medicare	900	58.5	293	76.1	
Not insured	28	1.8	–*	–*	
Other government	19	1.2	–*	–*	
Private insurance/managed care	464	30.2	61	15.8	
Education					.52
<20.9% No high school	1281	83.2	316	82.1	
>21% No high school	254	16.5	69	17.9	
Missing	–*	–*	–*	–*	
Income					.79
<$38,000	286	18.6	74	19.2	
≥$38,000	1249	81.2	311	80.8	
Missing	–*	–*	–*	–*	
Urban/rural					.52
Metro	1200	78.0	290	75.3	
Rural	41	2.7	11	2.9	
Urban	252	16.4	72	18.7	
Missing	46	3.0	12	3.1	
Distance (miles)					.24
≤12.5	726	47.2	195	50.7	
>12.5	809	52.6	190	49.4	
Missing	–*	–*	–*	–*	
Facility type					.61
Academic/research program	555	36.1	126	32.7	
Community cancer program	105	6.8	26	6.8	
Comprehensive community cancer program	632	41.1	171	44.4	
Integrated network cancer program	236	15.3	61	15.8	
Charlson-Deyo score					.004
0	818	53.2	171	44.4	
1	507	32.9	140	36.4	
2	141	9.2	43	11.1	
3	73	4.7	31	8.1	
Histology					.04
Adenocarcinoma	1044	67.8	236	61.3	
Other	38	2.5	14	3.6	
Squamous cell	457	29.7	135	35.1	
Subgroups					.23
ADN	413	26.8	104	27.0	
CWI	117	7.6	33	8.6	
TSZ	800	52.0	187	48.6	
Multiple	209	13.6	61	15.8	

Values are presented as mean ± SD or n (%). *S + CR*, Surgery followed by chemotherapy with or without radiation therapy; *S*, surgery alone; *ADN*, additional nodules in the ipsilateral lung, same lobe; *CWI*, chest wall invasion or resection; *TSZ*, tumor size >5 and ≤7 cm. *In accordance with the Data Use Agreement, cells <10 are prohibited from being reported.

in the context of pathologic N2 disease (pT3 N2) when guideline-concordant adjuvant systemic therapy is included after surgery. It is hypothesized that the use GCC where surgery is followed by adjuvant systemic therapy augments 5-year survival compared with surgery alone in pT3 N2 NSCLC, including at the level of individual T3 descriptors.

MATERIALS AND METHODS

Data Source

The National Cancer Database (NCDB) is a clinical oncology registry that collects de-identified information about patient demographic characteristics, treatment plans, and outcomes from more than 1500 Commission on Cancer-accredited treatment facilities. Approximately 70% of all patients diagnosed annually with cancer in the United States are captured in this registry.[7]

The NCDB Participant User File was used to query patients with pathologic T3 N2 M0 NSCLC disease from 2010 to 2016 (Figure 1). There were 1612 (83.8%) patients with R0 resection and the remainder had positive margins or were with missing data. In the NCDB, patients were staged using the seventh edition of the American Joint Commission on Cancer (AJCC) Staging Manual. In this study, they were restaged to the eighth edition per the criteria for tumor size, presence of additional nodules, and invasion. With respect to the criteria of invasion, T3 is defined as tumor that directly invades the chest wall, phrenic nerve, or pericardium.[4] Of note, the NCDB Participant User File does not distinguish between chest wall and parietal pleura invasion. Furthermore, it does not code for phrenic nerve or pericardial invasion. As such, the examination of T3 phenotype herein encompasses all features available for study through the NCDB. The National Comprehensive Cancer Network 2021 guide on clinical practice guidelines for NSCLC recommends systemic chemotherapy for patients with resected T3 N2 M0 disease.[5] The overall cohort of patients identified represent those who would be recommended this treatment protocol. Patients younger than age 18 years; with first treatment exceeding 60 days from diagnosis; with missing treatment information; carcinoid tumor histology; who did not undergo any surgery, chemotherapy, or radiation therapy; who had T3 disease that could not be categorized; and who received induction therapy with chemotherapy or chemoradiation therapy were also excluded. Secondary to the time frame of the study, those who were administered biologic therapies either in the neoadjuvant or adjuvant setting were excluded. Surgical treatment was defined as wedge resection, sublobar resection, lobectomy, or pneumonectomy. Patients who underwent adjuvant radiation therapy of any dose were included with a median dose of 36.0 Gray (interquartile range, 0-50.4 Gray). For those patients undergoing adjuvant therapy, only patients receiving multiagent therapy were included to be most consistent with GCC.

The cohort was selected using pathologic staging. This decision was made due to the fact that it would provide the most accurate assessment of the defining T3 descriptor and thereby allow for the creation of a purer cohort. With the same rationale, patients who received neoadjuvant therapy were excluded from the study. Furthermore, as it applies to the N2 status, the NCDB does not distinguish if noninvasive or invasive staging methods were used to determine clinical staging. Owing to the variability in invasive mediastinal staging, patients who underwent surgery as their initial therapy, and thus had a pathologic stage, were used to, again, create a more uniform cohort.

Patients were subsequently categorized into those who underwent definitive surgery alone (S) or who underwent definitive surgery with adjuvant chemotherapy with or without radiation (S + CR). Patients who underwent therapy in any other sequence or in isolation were excluded. The patients were further defined by the characterization of their T3 disease. Patients were categorized into 1 of 3 groups: with tumor size >5 and ≤7 cm (TSZ), with chest wall invasion (CWI), and with additional nodules in the ipsilateral lung, same lobe (ADN). The decision to focus the analysis of T3 characteristics on TSZ, CWI, ADN, and the presence of multiple T3 characteristics was done in view of the prohibitive sampling sizes that arose when examining for more specific permutations.

Variables and Outcomes

The primary outcome of interest was overall 5-year survival among the treatment cohorts, defined as the period from the date of diagnosis to the date of last known vital status. The survivorship start point was set to begin at the time of diagnosis to capture those patients for whom surgery was not the preferred primary therapeutic option. It has been demonstrated that treatment within 3 months of diagnosis does not significantly influence overall survival.[8] Patient demographic and socioeconomic status variables included age (continuous variable), gender, race (White, Black, Other), insurance type (Medicaid, Medicare, not insured, other government, private insurance), patient education (<20.9% no high school vs >21% no high school), patient income (≥$38,000 vs <$38,000), hospital urban versus rural status (metro, urban, rural), and distance to hospital (≤12.5 miles vs > 12.5 miles). Patient and hospital characteristics collected reflect zip codes associated with each entity, respectively. Clinical and tumor-specific variables included AJCC clinical staging, characterization of T3 disease, Charlson-Deyo comorbidity index score (0, 1, 2, ≥3), and histology type (adenocarcinoma, squamous cell, other). Facility type was categorized as academic/research program, community cancer program, comprehensive community cancer program, and integrated network cancer program.[9]

Statistical Analysis

Means and standard deviation were reported for continuous variables and analysis of variance was used for group comparisons. Frequencies and percentages were reported for categorical variables and χ^2 and Fisher exact test were used for between-group comparison when appropriate. Kaplan-Meier survival curves were generated and compared by log rank test to evaluate 5-year survival. Multivariable Cox regression was used to determine prognostic features for 5-year survival with T3 descriptors and treatment type as variables of interest. All other variables mentioned above were initially considered as covariates. Variables not acting as confounders

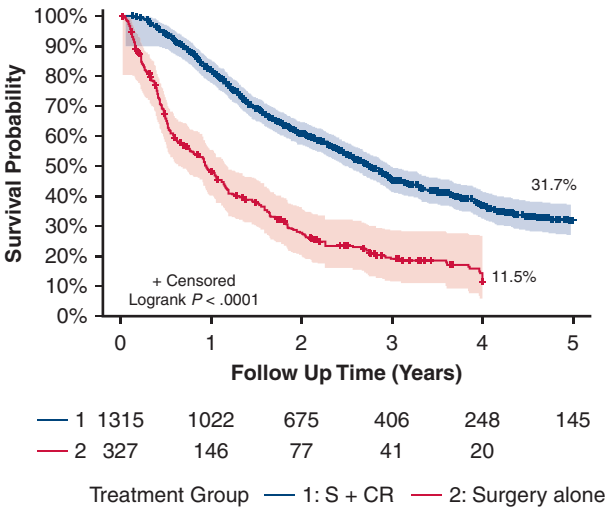
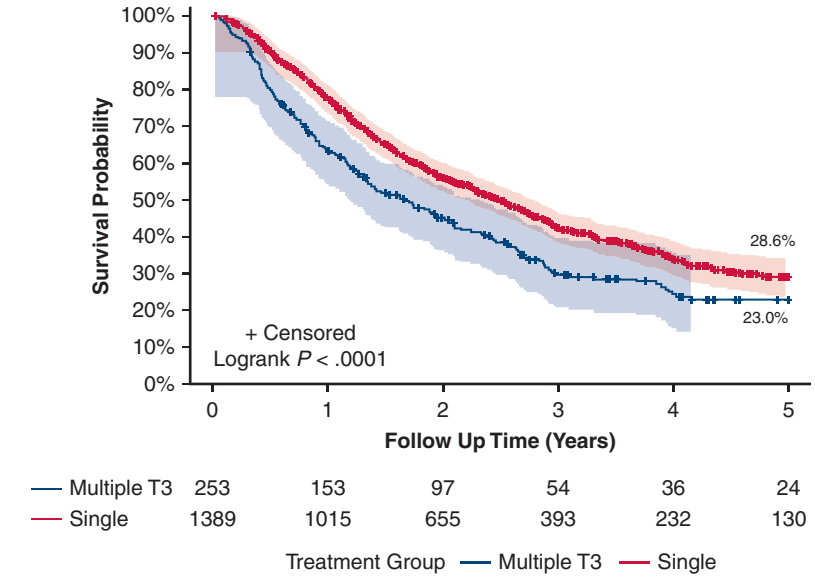


FIGURE 2. The overall survival for patients by treatment sequence alone was 31.7% at 5 years for surgery followed by chemotherapy with or without radiation (S + CR) and 11.5% at 4 years for surgery alone. Lines were truncated when the number of patients at risk fell fewer than 10 for the cohort. Shading above and below the lines drawn indicate 95% CI.



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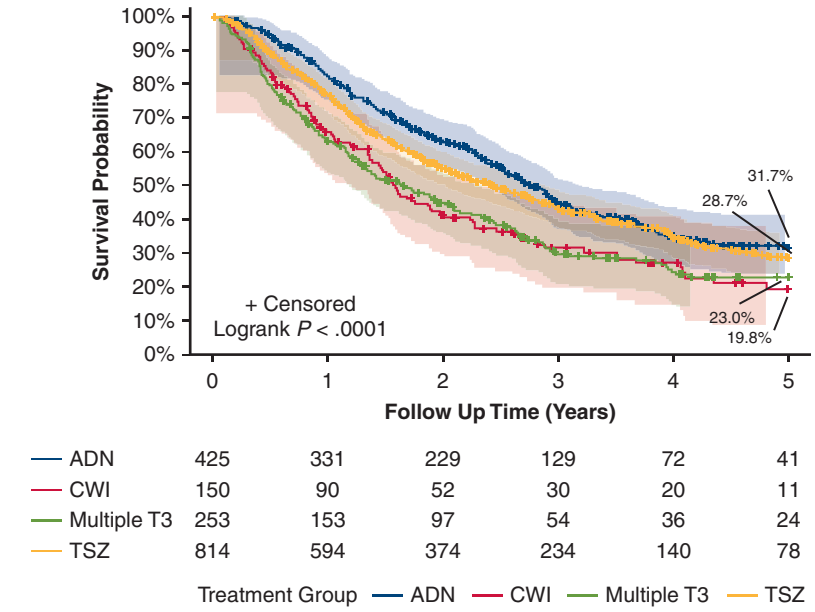

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FIGURE 3. The 5-year overall survival for patients by T3 disease characteristics. A, multiple T3 characteristics (23.0%) versus single T3 descriptor (28.6%). B, specific T3 characteristics (TSZ, 28.7%; CWI, 19.8%; ADN, 31.7%; multiple T3, 23.0%). Shading above and below the lines drawn indicate 95% CI. *TSZ*, Tumor size; *CWI*, chest wall invasion; *ADN*, additional nodule.

and with $P > .05$ were excluded from the final model using manual selection to avoid model overfitting. Confounders are predetermined as having more than 10% hazard ratio change treatment estimation. All statistical analyses were calculated using SAS version 9.4 (SAS Institute Inc).

The institutional review board or equivalent ethics committee of the University of Southern California approved the study protocol and publication of data (No. HS-16-00,906, approved on December 19, 2016).

RESULTS

Using the NCDB, 870,907 patients were identified to have been staged per the seventh edition of the AJCC staging manual (Figure 1). After exclusion criteria were applied, there were 1924 patients included in this study: S = 20.0% (n = 385) and S + CR = 80.0% (n = 1539). The demographic and clinical characteristics of these T3 N2 patients are shown in Table 1. With regard to T3 characterization, 51.3% (n = 987) had T3 disease characterized by TSZ, 7.8% (n = 150) by CWI, and 26.9% (n = 517) by ADN. Multiple T3 descriptors were found among 14.0% (n = 270) patients.

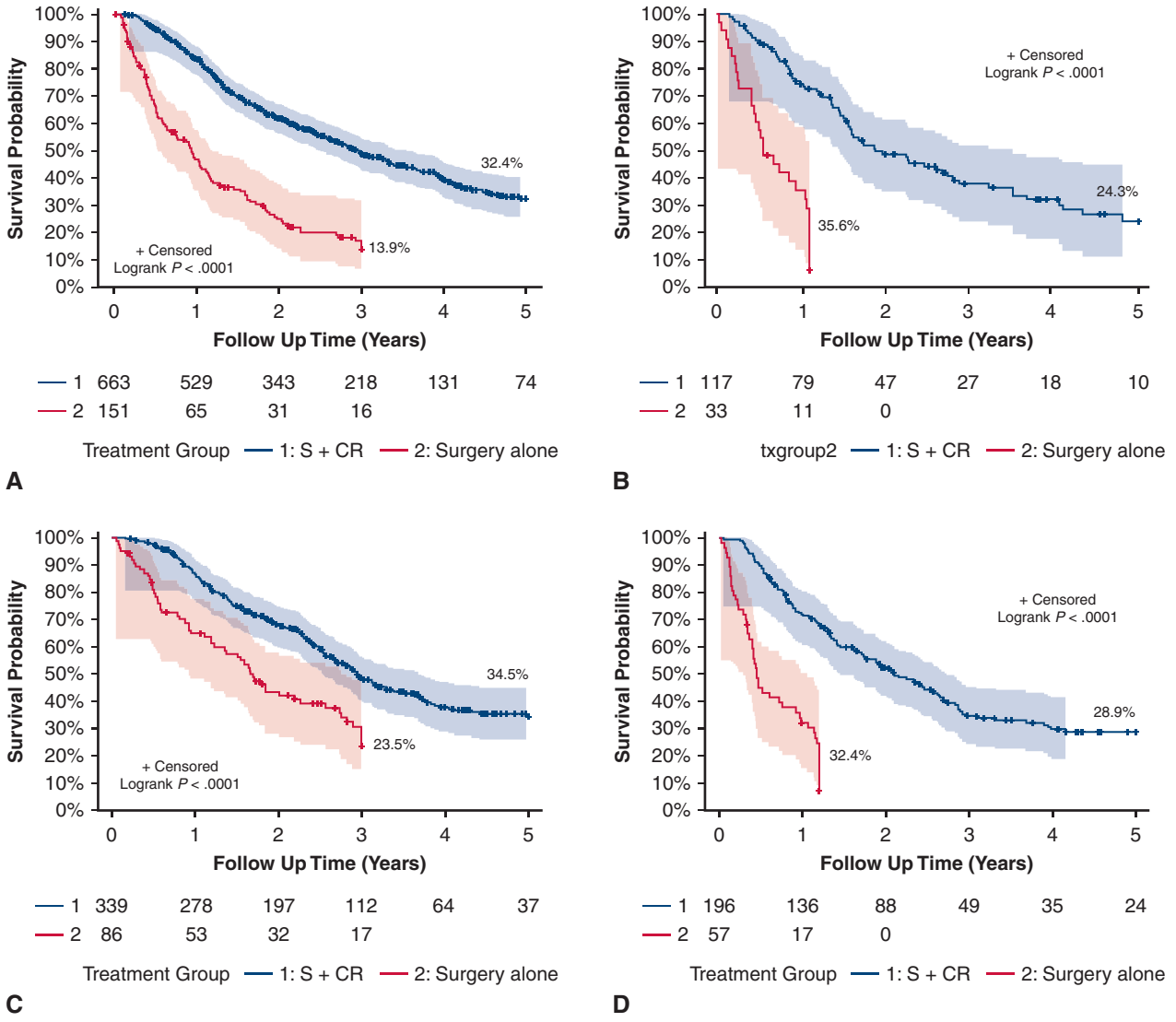


FIGURE 4. The overall survival when examining therapeutic modality in the context of specific T3 disease characteristics. Lines were truncated when the number of patients at risk fell fewer than 10 for the cohort. A, tumor size (surgery followed by chemotherapy with or without radiation [*S + CR*], 32.4%; surgery alone [S], 13.9%). B, chest wall invasion (S + CR, 24.3%; S, 35.6%). C, additional nodule (S + CR, 34.5%; S, 23.5%). D, multiple T3 characteristics (S + CR, 28.9%; S, 32.4%). Shading above and below the lines drawn indicate 95% CI.

The overall 5-year survival for patients in the cohort was 27.7%. The overall 5-year survival for patients who underwent S compared with those who S + CR was 11.1% and 31.7%, respectively ($P < .0001$) (Figure 2). Owing to reporting constraints with <10 patients, the 5-year overall survival for S could not be presented graphically. Overall survival was also calculated based on the T3 descriptors to evaluate whether or not differences in survival associated with either treatment approach were influenced by differences in T3 disease. Comparing disease characterized by single T3 descriptor versus multiple, overall survival was 28.6% versus 23.0% ($P < .0001$) (Figure 3, *A*). When looking at specific characteristics, the 5-year survival was 28.7% for those with TSZ, 19.8% for those with CWI, and 31.7% for those with ADN ($P < .0001$) (Figure 3, *B*). Survival outcomes for each T3 disease subgroup with respect to the treatment sequences received were further calculated. In all T3 subgroups, higher survival was seen with S + CR treatment compared with S: 32.4% versus 11.6% in TSZ, 24.3% versus 4.9% in CWI, and 34.5% versus 20.5% in ADN. This analysis was unable to be done for the multiple T3 cohort because no patient in the S treatment group made it to 5 years (Figure 4, *A-D*). Again owing to reporting constraints with <10 patients, the 5-year overall survival for S could not be presented graphically for the subgroups.

In the Cox proportional hazard model, comparing S with S + CR, the inclusion of adjuvant therapy to definitive

surgery was associated with higher overall survival in most T3 subtypes, including the presence of multiple T3 characteristics ($P < .001$) (Table 2). Increased risk was associated with age older than 68 years ($P < .001$) and Charlson-Deyo score above 2 ($P < .0001$). Decreased risk was associated with female gender ($P < .0001$) (Table 2).

TABLE 2. Association between patient characteristics and hazard of death

Variable	Hazard ratio (95% CI)	*P* value
T3 Characteristic treatment*		.005
TSZ		
S + CR	Reference	
S	2.59 (2.09-3.22)	<.0001
CWI		
S + CR	Reference	
S	2.91 (1.89-4.47)	<.0001
ADN		
S + CR	Reference	
S	1.58 (1.17-2.13)	.003
Multiple T3		
S + CR	Reference	
S	3.36 (2.41-4.69)	<.0001
Age (y)		
<61	Reference	
61-68	1.18 (0.97-1.44)	.09
68-75	1.42 (1.18-1.71)	.0002
>75	1.48 (1.22-1.78)	<.0001
Sex		
Male	Reference	
Female	0.73 (0.64-0.83)	<.0001
Charlson-Deyo score		
0	Reference	
1	1.255 (1.025-1.538)	.0283
2	1.168 (0.857-1.592)	.3248
≥3	1.679 (1.084-2.602)	.0204

TSZ, Tumor size >5 and ≤7 cm; *S + CR*, surgery followed by chemotherapy with or without radiation therapy; *S*, surgery alone; *CWI*, chest wall invasion or resection; *ADN*, additional nodules in the ipsilateral lung, same lobe. *Multivariable Cox regression, with the interaction term of T3 characteristic and treatment type.

DISCUSSION

The objective of this study was to evaluate whether or not specific T3 descriptors of NSCLC were associated with a more favorable response to a multimodal approach compared with definitive surgery alone in the context of N2 disease. The findings of this study demonstrate that the majority of patients with T3 N2 disease underwent treatment consistent with therapeutic recommendations according to international guidelines.[5] The recommended treatment for T3 N2 patients following definitive surgery with negative margins is to receive adjuvant or sequential chemotherapy with radiation therapy.[5] The results of the current study ultimately support guideline recommendations that surgery in the context of a multimodal therapeutic plan is associated with improved survival compared with surgery alone.

The novelty of the study rests in its granular approach to the different T3 descriptors in the context of surgically resected N2 disease. These results suggest that definitive S + CR, compared with S, may be beneficial, largely irrespective of the defining T3 feature associated with N2-nodal disease, which, at the present time, has not been studied previously. Of the T3 characteristics, the presence of additional nodules is what has been most studied, although not in the context of N2 disease, specifically.[10,11] Jeon and colleagues[12] examined the prognosis of each T3 descriptor for N0 through N2 disease and as defined by the seventh AJCC staging system, which has since been updated. Overall, the data presented herein may serve as a useful resource for thoracic surgeons and oncologists responsible for therapeutic decision making. The importance of a multimodal approach increasingly continues to be acknowledged, and the results presented here further suggest that such an approach may make a difference in T3 N2 disease irrespective of the ostensibly aggressive, defining T3 features.

Given the retrospective nature of this cancer registry study, it is important to recognize other limitations are associated with this study. First, the NCDB does not capture information regarding tissue confirmation, nodal bulkiness, and multistation nature of N2 disease, all of which contribute to N2 disease heterogeneity. Characterizing N2 disease is an important and nuanced realm where clinical expertise remains a crucial role in making the final decision in treating this stage of disease, particularly as it pertains to proceeding with surgery. Also, the NCDB does not distinguish between chest wall and parietal pleura invasion and does not code for phrenic nerve nor pericardial invasion. As such, the results presented herein must be interpreted in the appropriate context of T3 phenotypes. Second, the utilization of a pathologic T3 N2 cohort in lieu of a clinical cohort prevented the comparison of surgical to nonsurgical therapeutic approaches and alternative approaches using neoadjuvant therapies—all key issues with regard to this stage of disease. Although this exclusion precludes the generalizability of the study results to all patients with T3 N2 disease, the results provide additional support for the use of GCC irrespective of many T3 descriptors when N2 disease is confirmed. Also, without additional data, of which is currently unavailable through the NCDB, the improved survival for T3 patients with multiple nodules may reflect that some patients were presenting with synchronous primary lung cancers rather than a related malignancy. Furthermore, in conducting a comparative analysis between different treatment cohorts, it is important and necessary to risk adjust and best account for biases in patient selection. Given the nature of the present study, it was not possible to be privy to the collaborative decision-making process with regard to the treatment regimen

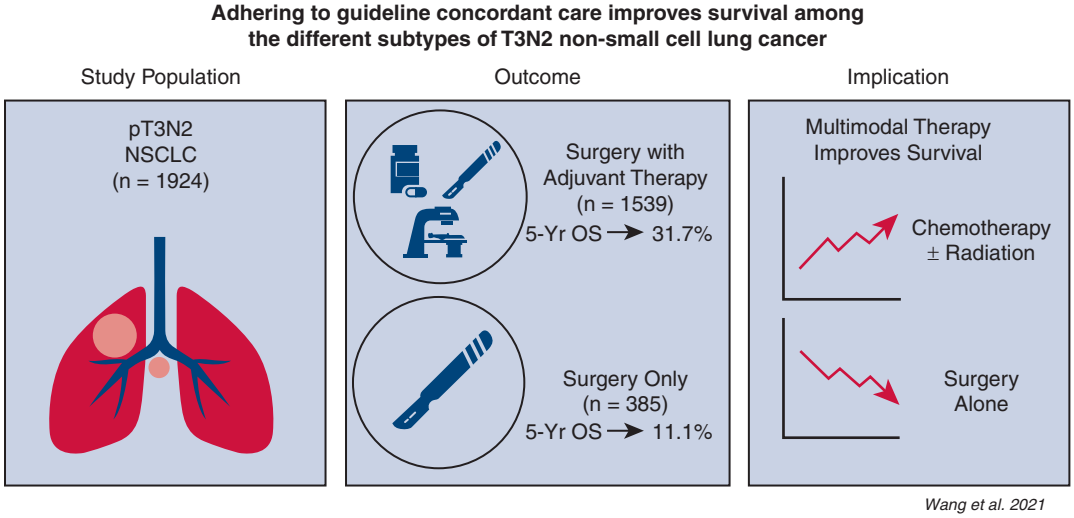
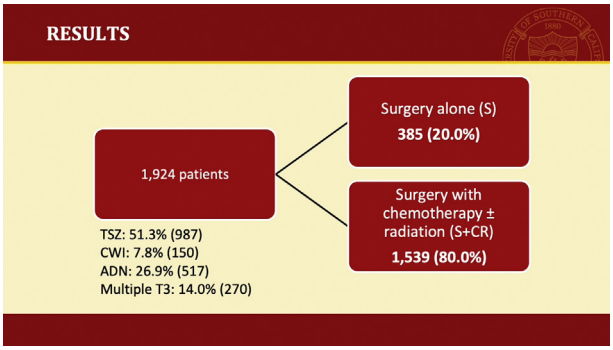


FIGURE 5. Graphical abstract depicting the study's methods, results, and implications. *T3N2*, T3 descriptor (tumor size, chest wall invasion, additional nodule) coupled with N2 (mediastinal lymph node involvement). *pT3N2*, Pathologic T3N2; *OS*, overall survival.

rendered and why a patient would not proceed to adjuvant therapy. However, in understanding that patient risk is a significant guiding factor, the risk of selection bias may be attenuated. The Charlson-Deyo score, although an imperfect measure, served as the best available and reliable measure to do so. The Charlson-Deyo comorbidity index is a variable encoded by the NCDB that represents a weighted sum of comorbidity burden, estimated using 15 comorbidities as described by Deyo and colleagues[13] in 1992, which includes but is not limited to renal disease, congestive heart failure, and moderate to severe liver disease. Scores range from 0 to 25, but because a small proportion of cases have scores >3, scores 3 to 25 are encoded as "3" in the database. To refine the analyses done, the Charlson-Deyo score was included as a covariate in all models. Lastly, it is recognized that current guidelines also recommend that osimertinib, a novel tyrosine kinase inhibitor, be considered as an adjuvant systemic therapy for T3 N2 disease.[5] The data from the current registry study did not allow for the delineation of which patients were administered agents that included osimertinib or other emerging therapies such as those from more recent landmark trials such as the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials or Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer trials, among other trials.[14,15] Although it is possible that some of these patients underwent adjuvant biologic therapies, it is unlikely that the results reflect the routine use of these agents uniformly, particularly in light of the fact that the study's time frame preceded the publication and wider acceptance of these therapies.



VIDEO 1. T3 N2 non–small cell lung cancer (NSCLC) treated with surgery followed by adjuvant therapy confers improved overall survival irrespective of T3 heterogeneity, strengthening the use of current guidelines for all T3 disease. Video available at: https://www.jtcvs.org/article/S2666-2736(22)00043-2/fulltext.

CONCLUSIONS

The use of clinical guidelines that recommend definitive S + CR for pathologic T3 N2 NSCLC disease, when compared with treatment with S, is associated with improved overall survival, largely irrespective of the T3 descriptor heterogeneity (Figure 5 and Video 1).

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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methodology employed, or the conclusions drawn from these data by the investigator.

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