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Pathological Downstaging Following Neoadjuvant Chemoimmunotherapy for Locally Advanced Lung Cancer

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Background/Research Objectives

Neoadjuvant chemoimmunotherapy (NCI) is becoming more common for patients with non-small-cell-lung cancer (NSCLC). However, optimal surgical management of cN2 disease which responds to NCI is unclear. We hypothesized that patients with NCI-associated pathological downstaging will have comparable long-term survival to stage-matched patients who did not require neoadjuvant therapies.

Methods

The National Cancer Database was used to identify patients with surgically treated NSCLC between 2004-2018. Rates of NCI and neoadjuvant chemotherapy (NC) were compared. Odds of pathological complete response (pCR) were evaluated with multivariable regression. Overall survival (OS) was examined with Cox models. Kaplan-Meier curves were used to evaluate pT-stage stratified outcomes.

Results

Overall, 358,276 patients were included. Of 2,597 (0.7% of total cohort) patients with clinical stage IIIA (cN2) disease who received systemic neoadjuvant therapies, 60 (2.3%) received NCI and 2,537 (97.7%) received NC.

NCI was associated with shorter intervals to surgery compared to NC (median 127 versus 137 days; p=0.02), higher rates of pCR (13.3% NCI vs 4.8% NC; p=0.003) (aOR 3.23, 95% CI 1.48-7.00), and improved OS (aHR 0.64, 95% CI 0.41-0.99 versus NC).

Patients with clinical stage IIIA (cN2) disease downstaged to ≤pT1aN0M0 after NCI and lobectomy (n=20) had 30-month OS comparable to ≤pT1aN0M0 patients treated with lobectomy or segmentectomy without neoadjuvant therapies (log-rank p=0.87 and p=0.91, respectively).

Table 1: Population characteristics of patients with resected clinical stage IIIA (cN2) NSCLC who received neoadjuvant systemic therapies

Parameter	Total N=2,597 %	Neoadjuvant Chemoimmunotherapy N=60 %	Neoadjuvant Chemotherapy N=2,537 %	P-value
Nodal Downstaging				0.89
No	49.1	50.0	49.1	
Yes	50.9	50.0	50.9	
Nodal Clearance				0.34
No	64.2	58.3	64.3	
Yes	35.8	41.7	35.7	
Pathological Complete Response				0.003
No	95.0	86.7	95.2	
Yes	5.0	13.3	4.8	

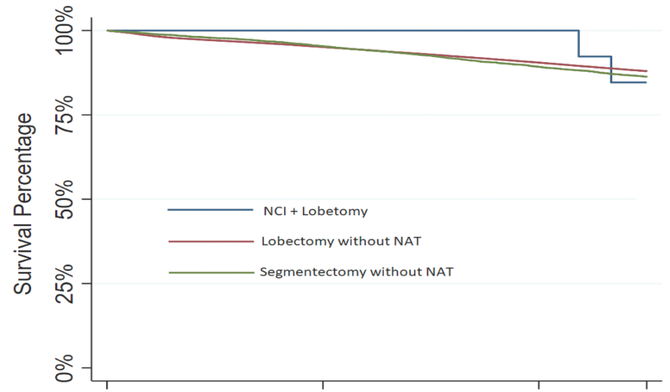
Table 2: Multivariable regression evaluating odds of nodal downstaging, nodal clearance, and pathological complete response among patients with resected clinical stage IIIA (cN2) NSCLC who received neoadjuvant systemic therapies

Parameter	Neoadjuvant Chemoimmunotherapy Odds Ratio (95% Confidence Interval)	Neoadjuvant Chemotherapy
Nodal Downstaging	0.98 (0.58-1.64)	Reference
Nodal Clearance	1.29 (0.76-2.19)	Reference
Pathological Complete Response	3.23 (1.48-7.00)*	Reference

Table 3: Cox Proportional Hazards Models evaluating overall survival among patients with resected clinical stage IIIA (cN2) NSCLC who received neoadjuvant systemic therapies

Parameter	Adjusted Hazard Ratio (95% Confidence Interval)
Chemoimmunotherapy	0.64 (0.41-0.99)*
Chemotherapy	Reference

Figure 1: Kaplan-Meier Curve Evaluating Overall Survival by Stage, Receipt of Neoadjuvant Chemoimmunotherapy, and Extent of Surgical Resection



Time (Months)	12	24	30
Patients at Risk	**N**	**N**	**N**
NCI + Lobectomy (n=20)*	20	14	10
Lobectomy without NAT (n=114,135)‡	105,654	94,694	87,025
Segmentectomy without NAT (n=8,249)‡	7,673	6,644	5,925

*Clinical Stage IIIA (cN2) downstaged to =pT1aN0M0 after NCI
‡Stage =pT1aN0M0 without neoadjuvant therapies

Conclusions

Neoadjuvant chemoimmunotherapy is associated with increased rates of pathological complete response compared to neoadjuvant chemotherapy alone. Further, patients downstaged to ≤pT1aN0M0 after neoadjuvant chemoimmunotherapy for stage IIIA (cN2) NSCLC may have similar overall survival outcomes compared to ≤pT1aN0M0 patients treated with lobectomy or segmentectomy who did not receive systemic neoadjuvant therapies. Future research should investigate whether locally advanced lung cancer downstaged after neoadjuvant therapy should receive segmentectomy if otherwise matching appropriate tumor size and location criteria.

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