

The 2026 American Association for Thoracic Surgery Expert Consensus Document: Evaluation and management of N2+ non-small cell lung cancer

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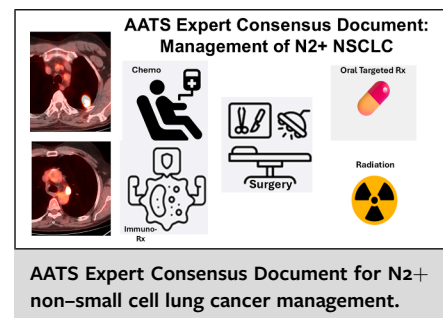
ABSTRACT

Objective: Multimodal therapy is recommended for the optimal treatment of N2 positive non-small cell lung cancer (NSCLC). Recent advancements in the use of immune checkpoint inhibitors and targeted therapy have dramatically changed the landscape of treatment. We reviewed recent trials and literature to develop consensus statements concerning the evaluation and treatment of potentially resectable NSCLC with N2 involvement.

Methods: The American Association for Thoracic Surgery Clinical Practice Standards Committee assembled an international panel of medical oncologists, radiation oncologists, radiologists, and thoracic surgeons. A focused literature review was performed with the assistance of a medical librarian. The panel used a modified Delphi method to develop expert consensus statements with class of recommendation and level of evidence on issues related to the treatment of potentially resectable N2 positive NSCLC.

Results: Consensus was reached on 13 statements on topics related to staging, determinants of unresectable disease, use of chemoimmunotherapy or targeted therapies, proper use of neoadjuvant and/or adjuvant therapy, restaging, and the safety of resection after chemoimmunotherapy.

Conclusions: NSCLC with N2 disease remains a challenging, heterogeneous disease. These expert consensus recommendations are meant to provide guidance to identify appropriate surgical patients and to formulate the best multimodality treatment of patients with N2-positive NSCLC. (J Thorac Cardiovasc Surg 2026; ■:1-17)



CENTRAL MESSAGE

Optimal treatment of N2-positive NSCLC requires accurate staging, determination of resectability and multidisciplinary input.

PERSPECTIVE

Locally advanced lung cancer remains challenging to cure. stage III N2+ NSCLC has traditionally been treated with multimodality therapy, incorporating surgery for resectable patients and definitive chemoradiation for unresectable. Newer therapies yield better systemic control, making it critical to determine the optimal local therapy for patients with N2+ disease. Surgery may have an expanded role in this new era.

See Commentary on page XXX.
See Discussion on page XXX.

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Abbreviations and Acronyms

AATS	= American Association for Thoracic Surgery
AEGEAN	= Phase 3 Clinical Trial Evaluating the Use of Neoadjuvant Durvalumab Plus Chemotherapy Followed By Adjuvant durvalumab in the Treatment of NSCLC
CheckMate	= Checkpoint Pathway and Nivolumab Clinical Trial Evaluation
CoR	= class of recommendation
CT	= computed tomography
EBUS	= endobronchial ultrasound
EFS	= event-free survival
FDG-PET	= fluorodeoxyglucose positron emission tomography
IASLC	= International Association for the Study of Lung Cancer
KEYNOTE	= clinical development program and naming convention for studies evaluating pembrolizumab
LoE	= level of evidence
NADIM	= Phase II Clinical Trials Investigating Neoadjuvant Nivolumab Combined With Chemotherapy for Resectable Stage III NSCLC
NCCN	= National Comprehensive Cancer Network
NSCLC	= non-small cell lung cancer
pCR	= pathologic complete response
STS	= Society of Thoracic Surgeons



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Non-small cell lung cancer (NSCLC) remains among the most lethal malignancies worldwide with advanced and locally advanced disease accounting for most deaths.¹ Complete surgical resection remains the mainstay of curative therapy for localized NSCLC as stand-alone therapy for

early-stage disease and as part of multimodality therapy for locally advanced disease. In the past, all operable patients believed to have resectable disease had upfront surgery. However, it was clear that patients with N2 disease had dismal survival, particularly with local therapy alone.² This led to the use of neoadjuvant chemotherapy or chemoradiotherapy with modest success.^{3,4} Recent advances in molecular characterization of tumor and development of targeted and immunotherapies have resulted in several clinical trials demonstrating significant improvements in disease-free and overall survival with utilization of individualized therapies in combination with surgery.⁵⁻¹⁰ This progress in lung cancer management has made decision making regarding resectability, timing, and type of perioperative therapy and surgical considerations more complex. This American Association for Thoracic Surgery (AATS) Expert Consensus Document utilizes a multidisciplinary group of lung cancer clinicians to provide recommendations on the ideal assessment and treatment of patients with stage III, N2 disease.

METHODS

This expert consensus process was conducted in line with the joint AATS and Society of Thoracic Surgeons (STS) statement on producing clinical practice guidelines.¹¹ The AATS Clinical Practice Standards Committee initiated this Expert Consensus Document on the evaluation and management of N2-positive NSCLC and assembled this writing group of experts. All authors contributed to the drafting of this document and have completed conflict of interest disclosures ([Online Data Supplement](#)). This multidisciplinary committee consists of 14 thoracic surgeons, 2 medical oncologists, 1 radiation oncologist, and 1 radiologist, representing 14 different institutions across 3 continents.

Formulation of Clinical Questions, Literature Review, and Evidence Synthesis

Following the creation of the writing group, a literature review was conducted with the aid of librarians trained in systematic review methodology. The search terms and strategy are detailed in [Table E1](#). We developed search strategies that incorporated keywords and Medical Subject Headings related to stage III NSCLC, N2 disease, resection, neoadjuvant therapy, and multimodal treatment approaches, including immunotherapy, radiotherapy, and imaging/staging. Searches were limited to studies published in English since January 2005. Themes and concepts were prioritized based on clinical relevance and ambiguity, and an organizational framework was created. This framework included the development of

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3 subgroups: defining resectability of N2 disease, considerations for perioperative systemic therapy, and surgical management following neoadjuvant therapy. Each subgroup met several times individually to create relevant questions according to the population/patient/problem, intervention, comparison, and outcome format. Literature searches were conducted on a regular basis between January 2025 and October 2025, inclusive of publications between 2005 and 2025. Members of each subgroup screened the titles and abstracts of the search results for relevance and extracted and synthesized the information from these selected articles. Evidence-based recommendations were then formulated within subgroups throughout multiple rounds of writing and revisions. The quality of evidence and language for each statement was chosen to be consistent with that recommended in the harmonizing guidelines consensus document by the AATS, European Association for Cardio-Thoracic Surgery, European Society of Thoracic Surgeons, and STS¹¹ (Figure 1).

The Delphi Method

Development of this expert consensus document was conducted utilizing the modified Delphi method. Within subgroups, each recommendation was voted on utilizing a survey with a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, and 5 = strongly agree). We determined *a priori* that a response rate of at least 80% was required, with a minimum of a 75% agreement rate to define consensus. Several rounds of surveys were conducted within each subgroup, followed by revisions, until consensus was reached on each statement. Discussions regarding the relevant details, evidence, and references for each statement were held throughout this process. The entire working group had the opportunity to comment on each recommendation before publication.

RESULTS

A summary of all statements with class of recommendation (CoR), level of evidence (LoE), and panel consensus is listed in Table 1.

Statement 1: Incomplete (R1/R2) Resection in Patients with N2 NSCLC Is Associated With Poor Survival. It Is Recommended That Every Attempt Is Made to Achieve an R0 Resection (CoR I, LoE B-nonrandomized)

Incomplete resection (R1 [microscopic residual tumor at margin]; R2 [macroscopic residual tumor at margin]) among patients with pathologic N2 NSCLC is strongly associated with inferior overall survival and other negative oncologic outcomes compared with complete (R0 [no residual tumor at margin]) resection. Validation studies based on the International Association for the Study of Lung Cancer (IASLC) residual tumor classification have consistently demonstrated

a stepwise decline in survival with increasing tumor burden, with R(un) (uncertain margin status), R1, and R2 status representing progressively worsening prognosis. In their 2021 study, Yun and colleagues¹² confirmed that IASLC R descriptors provided strong prognostic stratification, particularly among patients with N2 disease, where R1 or R2 resections were significantly associated with poorer outcomes. A later study further reported a significantly increased risk of recurrence (hazard ratio [HR], 1.50; 95% CI, 1.17-1.52) and death (HR, 1.51; 95% CI, 1.17-1.96) among patients with R1 or R2 resections compared with R0.¹³ These findings are concordant with the IASLC Lung Cancer Staging Project's analysis of more than 14 000 cases, which demonstrated a graded decrease in median survival from R0 resections (70 months) to R1 (50 months) and R2 (30 months) resections among patients with N2 disease.¹⁴

This survival pattern highlights that residual disease not only represents a technical operative outcome but may also reflect aggressive underlying tumor biology and mediastinal involvement. Previous studies have established that incomplete resection is often associated with adverse pathologic features such as advanced tumor stage, multistation nodal involvement, and extracapsular extension, among others, features which have been consistently linked with aggressive disease and decreased responsiveness to multimodality therapy.¹⁵⁻¹⁸ Clinical data have similarly shown that patients harboring these high-risk features experience significantly poorer survival after resection, even after multimodal management.^{16,17} The demonstrated prognostic implications of residual disease emphasize the importance of prioritizing an R0 resection when considering surgical candidacy in patients with potentially resectable N2 NSCLC.

As modern trimodality therapy and perioperative immunotherapy continue to evolve, complete operative resection assumes an even more critical role in optimizing patient outcomes. Lee and colleagues¹⁹ demonstrated that the most important prognostic factor for progression-free survival in N2-positive stable IIIA NSCLC treated with neoadjuvant chemoradiation followed by surgery was the posttreatment pathologic nodal status ($P < .001$), rather than the initial bulk or extent of mediastinal nodal disease. Survival benefits are largely confined to patients who attain appropriate mediastinal response and complete clearance. Recent Phase 3 trials in resectable node-positive NSCLC, including the Phase 3 Clinical Trial Evaluating the Use of Neoadjuvant Durvalumab Plus Chemotherapy Followed by Adjuvant Durvalumab in the Treatment of NSCLC (AEGEAN) and KEYNOTE (the clinical development program and naming convention for studies evaluating pembrolizumab) 671 trials, have demonstrated that the addition of perioperative immunotherapy may also improve event-free survival (EFS) and pathological complete response (pCR) rates compared with chemotherapy alone; however, these benefits have primarily been reported in the context of relatively high rates of complete resection.^{6,7}

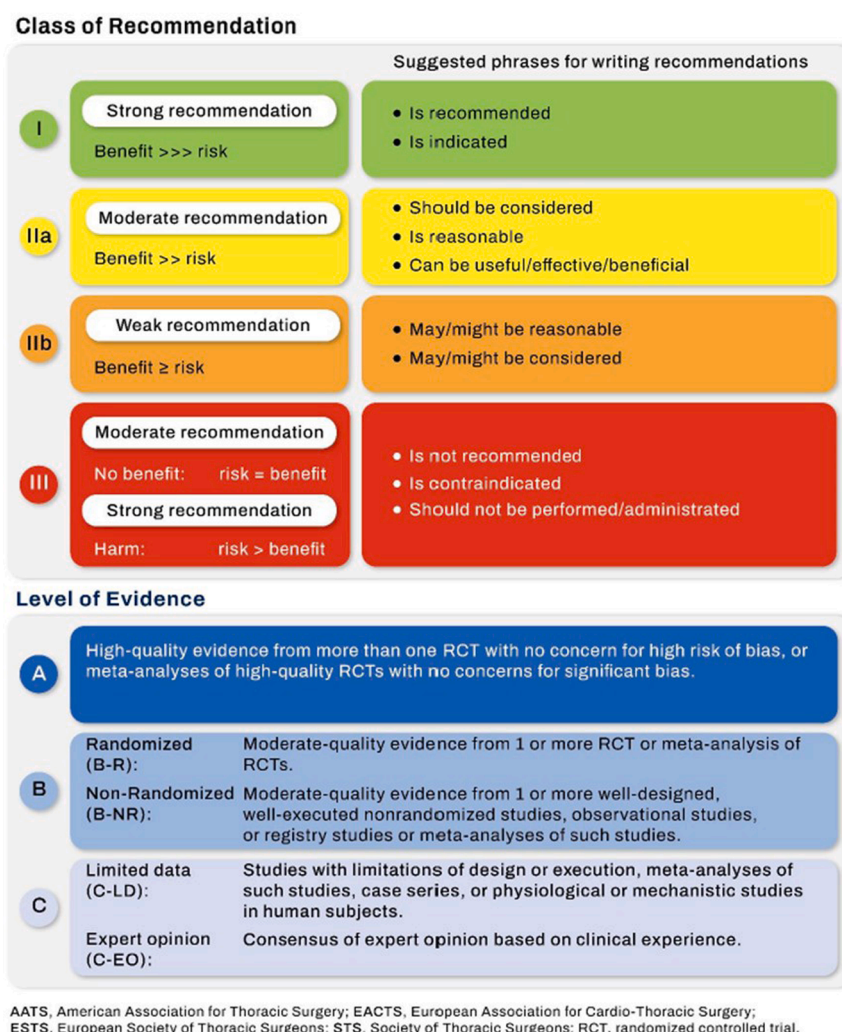


FIGURE 1. Adopted definitions of classes of recommendation and levels of evidence. Adapted from reference.¹¹ RCT, Randomized controlled trial.

In the absence of complete resection, the benefit of adjuvant chemoimmunotherapy is less clear. Analyses of large databases have consistently shown that the survival benefit of multimodality therapies is contingent on achieving R0 resection. In a 2015 study, Hancock and colleagues²⁰ demonstrated that although postoperative chemotherapy and radiation were associated with superior survival outcomes across all stages of NSCLC, neither was consistently associated with improved outcomes among patients with incomplete resections.

Emerging data on the influence of incomplete resection in the setting of neoadjuvant chemoimmunotherapy are available in abstract form. These results were described for Checkpoint Pathway and Nivolumab Clinical Trial Evaluation (CheckMate) 816. In this trial, specifically in stage III

patients, R0 resection was accomplished in 87.6%, with the remainder as R1 resection. Overall survival outcomes by resection status for stages IB to III, on the treatment arm, at 5 years, was 75% for R0 and 62% for R1.²¹

Altogether, these findings suggest that operative resection for N2 NSCLC should be pursued primarily when a realistically achievable R0 resection is anticipated, following rigorous staging, multidisciplinary consideration, and, where appropriate, perioperative systemic therapies. In patients for whom complete resection is unlikely, such as in the case of extensive multistation or bulky nodal disease, or extranodal extension, definitive nonsurgical approaches may provide a more appropriate therapeutic alternative, thus minimizing the perioperative risks of a procedure unlikely to confer a meaningful survival benefit.

TABLE 1. Summary of statements, class of recommendation (CoR), level of evidence (LoE), and approved consensus from panel members for management of N2+ non-small cell lung cancer (NSCLC)

	Statement	CoR	LoE	Approved consensus (%)
1	Incomplete (R1/R2) resection in N2 NSCLC patients is associated with poor survival. It is recommended that every attempt is made to achieve R0 resection.	I	B-NR	100
2	The determination of resectability, involving a surgeon experienced in thoracic oncologic surgery, should be made before initiation of therapy.	IIa	C-EO	83
3	In patients with locally advanced NSCLC (cT2a or greater, cN1, cN2), pathologic mediastinal staging (endobronchial ultrasound or cervical mediastinoscopy) is recommended pretreatment to verify the presence of N2 disease and rule out N3 disease	I	B-NR	100
4	Resection can be beneficial in select T4 N2 patients. Multidisciplinary discussion of these patients should be performed before determination of treatment.	IIa	C-LD	100
5	In addition to FDG-PET/CT scan, patients with suspected N2 disease should undergo diagnostic contrast-enhanced CT chest before determination of treatment	IIa	B-NR	100
6	Direct extension of tumor in continuity with bulky mediastinal nodal disease should be considered unresectable	IIa	C-LD	80
7	Multistation N2 disease with nodes >3 cm or invasion to adjacent structures should be considered unresectable	IIa	C-LD	80
8	It is recommended that patients with NSCLC with clinical or pathological N2 disease and actionable <i>EGFR</i> or <i>ALK</i> mutations receive targeted therapy as opposed to induction chemoimmunotherapy	I	B-NR	87
9	The degree of benefit derived from adjuvant immunotherapy in patients who have received neoadjuvant chemoimmunotherapy is unclear. Omission of adjuvant immunotherapy may be considered in patients with pCR, especially in those who have had complications from such treatment in the neoadjuvant setting.	IIb	B-NR	93
10	Routine pathologic restaging should not be performed unless there is concern for the presence of new N3 or M1 disease	III	C-EO	100
11	For medically operable patients with resectable N2 NSCLC, the rates of treatment-related adverse events during neoadjuvant treatment with chemo-immunotherapy are low, and the majority of patients undergo surgical resection without significant delay.	I	B-NR	100
12	Surgical resection can be performed safely after neoadjuvant chemo-immunotherapy in patients with resectable N2 NSCLC, with low rates of pneumonectomy and high rates of R0 resection.	IIa	B-NR	93
13	For medically operable patients with resectable N2 NSCLC disease, and without actionable <i>EGFR</i> or <i>ALK</i> mutations, neoadjuvant chemoimmunotherapy is preferred over neoadjuvant chemotherapy to optimize both pathologic response and long-term survival.	I	A	100

NR, Nonrandomized; EO, expert opinion; LD, limited data; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; pCR, pathologic complete response.

Statement 2: The Determination of Resectability, Involving a Surgeon Experienced in Thoracic Oncologic Surgery, Should Be Made Before Initiation of Therapy (CoR IIa, LoE C-expert opinion)

Among thoracic surgeons, there are no universally accepted criteria for differentiating unresectable from resectable NSCLC. Surgeon and institutional experience greatly influence resectability and may vary across centers. The term *operability* differs from resectability and is often used to define patient surgical fitness and cardiopulmonary reserve. The pillars of resectability have traditionally been defined by anatomical factors such as the extent of local invasion (T stage), lymph node involvement (N stage), and the ability to achieve complete resection (R0) with negative margins. Controversy exists among surgeons and centers regarding the presence of multistation N2 disease, bulky N2 disease, and T4 invasion.^{22,23} Advancements in modern therapies such as neoadjuvant chemoimmunotherapy or targeted therapy for locally advanced NSCLC, where biologic response to treatment may change resectability, are challenging surgical dogma.^{5,6,8,24}

Certain patients may have a dramatic response to neoadjuvant chemoimmunotherapy. Several members of the writing committee raised the possibility of whether patients with borderline resectable disease may be treated with several cycles of neoadjuvant chemoimmunotherapy and reassessed for resectability. The 83% consensus on this statement reflects this concern. The multi-disciplinary team)-Bridge study is a Phase 2 trial across 57 international centers involving patients with stage IIB to IIIB NSCLC deemed resectable or borderline resectable by their local multidisciplinary panel. Patients receive 2 cycles of platinum-based chemotherapy and durvalumab. Those patients deemed resectable then receive an additional 1 or 2 cycles before resection, followed by adjuvant durvalumab, whereas those deemed unresectable receive definitive chemoradiation followed by adjuvant durvalumab. The primary end point is the number of patients who undergo resection, and pCR.²⁵ Preliminary data reported in abstract form indicate that 71% of borderline patients are indeed resectable after neoadjuvant therapy, with an R0 resection rate of 85%.²⁵ A multicenter retrospective series similarly reported success with borderline-resectable patients receiving neoadjuvant chemoimmunotherapy with 75% ultimately able to undergo surgery.²⁶ These preliminary data suggest that the decision for surgery could be made based on response to neoadjuvant therapy rather than before therapy. The panel believed that the data were not sufficiently mature at this time to make this recommendation.

Board-certified thoracic surgeons who perform lung cancer surgery as a predominant part of their practice should play a major role in determining surgical resectability of NSCLC, as endorsed by the NSCLC panel of the National

Comprehensive Cancer Network (NCCN), American College of Chest Physicians clinical practice guideline, and the STS expert consensus on multidisciplinary management of resectability of locally advanced NSCLC.²⁷⁻²⁹ This consensus should involve an in-person meeting between the surgeon and patient before determination of therapy. Although resectability can often be determined by radiologic studies, key aspects of operability, such as frailty, require an in-person consultation. Studies of the relationship between surgeon specialty and patient outcome found that board certification and general thoracic surgical practice were associated with a 23% lower risk of operative mortality compared with surgeons without American Board of Thoracic Surgery certification.^{30,31} Thoracic surgeons should be involved in the decision-making process from the outset in collaboration with a multidisciplinary tumor board inclusive of thoracic-focused medical and radiation oncologists.³² Adherence to guideline-specific treatment of locally advanced NSCLC is best achieved on a multidisciplinary tumor board.³³

Statement 3: In Patients With Locally Advanced NSCLC (cT2a or greater, cN1, or cN2), Pathologic Mediastinal Staging (Endobronchial Ultrasound or Cervical Mediastinoscopy) Is Recommended Pretreatment to Verify the Presence of N2 Disease and Rule Out N3 Disease (CoR I, LoE B-nonrandomized)

Clinical staging based on radiographic imaging alone for patients with NSCLC remains relatively inaccurate.³⁴⁻³⁶ Patients who have clinical evidence of locally advanced NSCLC with nodal involvement should undergo pathologic mediastinal staging. Suspicion of nodal involvement by computed tomography (CT) (size criteria) or by fluorodeoxyglucose-positron emission tomography (FDG-PET) (FDG avidity or increased standard uptake value) mandates pathologic mediastinal and hilar staging to confirm the presence of metastatic disease histologically in the nodes and verify clinical N stage. Pathologic staging to diagnose N1 disease and accurately distinguish between N2 disease and N3 disease is crucial in determining the appropriate treatment plan.

False positive results from imaging may suggest nodal involvement and incorrectly upstage the patient without tissue confirmation. FDG avidity in the lymph nodes may be due to a number of benign etiologies, including infections and inflammatory processes (including granulomatous disease, sarcoidosis), and reactive processes (such as postobstructive response). In 1 study, comparing PET versus CT for staging in lung cancer for mediastinal staging in lung cancer, patients were incorrectly upstaged by PET in 5% of cases.³⁷ In another study, comparing clinical to pathologic staging of the mediastinum, clinical staging in tumors without cN involvement missed nearly 20% of patients with cN1 or cN2.³⁸ Randomized trial data have suggested

that the positive predictive value of PET was only 64%. In this study, among patients who had clinical N2 or N3 involvement by PET, there was a 36% false positive rate.³⁹ Others have reported similarly poor positive predictive values for PET, as low as 38%.⁴⁰⁻⁴²

Making treatment decisions based on a presumption of mediastinal nodal involvement of imaging alone without tissue confirmation could potentially result in a patient being given neoadjuvant therapy unnecessarily, or perhaps erroneously denying an opportunity for a potentially curative resection. Pathologic mediastinal staging for tissue confirmation in these patients has been recommended in multiple guidelines issued by the American College of Chest Physicians and NCCN.⁴³⁻⁴⁶

Staging of the mediastinal and hilar stations bilaterally is important to rule out N3 disease. The rate of occult N3 metastasis was more than 50% in patients with clinical N2 disease in 1 study, with multistation disease and larger T size (T3, T4) noted as risk factors for occult N3 disease.⁴⁷ N3 nodes exist beyond the scope of what can be surgically resected and patients with N3 involved nodes should not be considered for surgical resection outside of a clinical trial. Patients with N3 disease have been excluded from almost all prior neoadjuvant/adjuvant trials involving locoregionally advanced NSCLC. There is currently one active trial, Neoadjuvant Chemo-Immunotherapy and Surgical Resection in Locally Advanced NSCLC with N3 Lymph Node Involvement NCT 06449313.⁴⁸

Mediastinoscopy has historically been considered the gold standard modality for pathologic staging, but endobronchial ultrasound (EBUS) with transbronchial needle aspiration has largely supplanted mediastinoscopy in current practice as the initial modality of choice. Diagnostic yield and accuracy for EBUS have been demonstrated to be comparable, or even superior, to mediastinoscopy.⁴⁹⁻⁵³ EBUS is able to access hilar N1 disease in patients who may benefit from neoadjuvant treatment. These results, coupled with its less invasive nature, have led to the adoption of EBUS as the first line modality of pathologic mediastinal staging. Mediastinoscopy may be considered when EBUS biopsy of a suspicious node is nonconfirmatory of clinically positive disease.⁵⁴⁻⁵⁷

Statement 4: Resection Can Be Beneficial in Select Patients With T4 N2 Disease. Multidisciplinary Discussion of These Patients Should Be Performed Before Determination of Treatment (CoR IIa, LoE C-limited data)

NSCLC may be staged as T4 in 1 of 3 categories: size >7 cm, additional tumor nodule in an ipsilateral lobe, or local invasion of certain structures. Perioperative trials randomizing patients to neoadjuvant chemoimmunotherapy versus neoadjuvant chemotherapy alone included stage IIIB (T4) patients. In KEYNOTE-671, 27.5% of patients had T4 disease, 44% of

patients had N2 disease, and 15% were stage IIIB. The benefit in overall survival was not significantly different between the IIIA and IIIB subgroups (HR, 0.69-0.74).^{7,24} Twenty-five percent of the patients in the AEGEAN trial were T4, and 24% were stage IIIB, although patients categorized as T4 for any reason other than >7 cm size were excluded.⁶ Check-Mate 77T included T4 patients and stage IIIB (N2) patients but did not detail the number of T4 patients nor those who were T4N2.⁸ Phase II Clinical Trials Investigating Neoadjuvant Nivolumab Combined With Chemotherapy for Resectable Stage III NSCLC (NADIM II), a trial for stage III only, excluded patients with T4 N2 disease.⁵⁸ R0 resection was approximately 90% in these trials, indicating that selection of these patients for surgical resection was appropriate. The lack of detail as to the type of T4 disease and how many patients were T4 N2 made it difficult to draw precise conclusions regarding the benefit in this subgroup of patients.

In a review of the National Cancer Database, Stiles and colleagues examined T3-T4 N2 patients between 2010 and 2019 treated with multimodal surgery and performed a propensity score matched analysis among those undergoing surgery and not undergoing surgery.^{59,60} In this study, 78% of patients were T4 and 22% were T3. Only 9% of patients overall had surgery, and only 38% of those received preoperative radiation. Thirty-day mortality was 1.5%, and margins were negative in 83% of patients. Those who underwent surgery had fewer than 2 comorbidities, were more likely to be treated at an academic center and had different income and insurance status. After propensity score matching, patients who had surgical resection had better overall survival (HR, 0.48; 95% CI, 0.46-0.51) and median overall survival (51.3 vs 19.8 months; $P < .001$) than those treated with definitive chemoradiation. There certainly continues to be the possibility of uncorrected bias in the analysis, and it should be noted that this cohort was treated prior to the era of neoadjuvant chemoimmunotherapy.

The expert consensus group believed that it is reasonable to consider resection in patients with T4 N2 based on tumor diameter >7 cm, when R0 resection is likely based on tumor location. Moreover, patients who are T4 N2 by virtue of local invasion of structures which can be resected with limited additional morbidity (a small portion of left atrium, vagus nerve, diaphragm, or with limited invasion of vertebral body) should be discussed at tumor board for consideration of resection. Resection in patients with involvement of other structures (superior vena cava, trachea, or recurrent laryngeal nerve) that may carry higher morbidity would need to be considered cautiously. Patients with N2 and with T4 invasion into structures carrying a high risk of morbidity such as aorta, esophagus, and spinal canal should probably not be considered for resection. Patients with T4 staging based on multilobar disease with N2 disease, who would most likely require pneumonectomy, can be considered for resection after multidisciplinary discussion before and after neoadjuvant therapy.

Statement 5: In Addition to FDG-PET/CT Scan, Patients With Suspected N2 Disease Should Undergo Diagnostic Contrast-enhanced CT Chest Before Determination of Treatment (CoR IIa, LoE B-nonrandomized)

The evaluation of suspected N2 NSCLC requires accurate radiologic staging to determine appropriate treatment and feasibility of resection. Both metabolic and anatomic characterization contribute to the assessment of mediastinal nodal involvement. Although FDG-PET is an important component of initial noninvasive staging, it does not obviate the need to obtain chest CT with intravenous contrast, which offers greater anatomic detail with thin-slice axial images compared with the attenuation correction CT images provided with PET/CT. The American College of Radiology Appropriateness Criteria include the recommendation for chest CT with intravenous contrast for initial noninvasive staging of patients with known or suspected NSCLC.⁶¹ Noncontrast chest CT is an alternative for patients with a history of prior severe allergic reaction to iodinated contrast. Chest CT with intravenous contrast provides optimal anatomic characterization of lymph node size and morphology. Contrast enhancement helps delineate lymph node borders with vascular structures and may assist in predicting the need for advanced intraoperative surgical maneuvers (pulmonary artery control or need for cardiopulmonary bypass) and/or extended pulmonary resections such as sleeve resections or pulmonary artery angioplasty. CT has limitations in the assessment of mediastinal nodal disease; when a positive lymph node is defined as measuring >1 cm in short axis, the sensitivity of chest CT is 55%, and the specificity is 81%.⁴⁵ Additional CT features that may raise clinical suspicion for disease include abnormal enhancement of a lymph node, central necrosis, and loss of a fatty hilum.

FDG-PET imaging adds metabolic characterization but also has recognized limitations. False-positive FDG avidity may occur in granulomatous or other inflammatory conditions, whereas false-negative uptake is seen in indolent tumors, including lepidic adenocarcinoma and carcinoid tumors.^{34,62,63} Studies comparing FDG-PET, CT, and combined PET/CT demonstrate improved accuracy with integrated imaging, although sensitivity and specificity for mediastinal nodal disease remain imperfect.^{64,65}

PET-CT following neoadjuvant chemoimmunotherapy; that is, for restaging, may aid in predicting the likelihood of pCR and can be useful in intraoperative decision making. An analysis of 39 patients receiving PET-CT before and after neoadjuvant chemoimmunotherapy showed that a 70% reduction in maximal standardized uptake value significantly correlated with pCR (area under the curve, 0.89; $P = .01$).⁶⁶

The combination of PET and diagnostic contrast-enhanced CT supports multidisciplinary treatment planning by ensuring accurate staging and resectability assessment.

The use of CT chest with intravenous contrast along with PET is useful to guide discussions regarding induction therapy, surgical candidacy, and expected operative approach.⁶⁷ This recommendation is designated Class IIa, Level B-nonrandomized because available evidence, although not randomized, consistently demonstrates improved staging accuracy and clinical decision making when contrast-enhanced CT is obtained in addition to FDG-PET supporting a recommendation based on clinical practice and consensus interpretation of available data.

Novel imaging modalities, including PET/magnetic resonance imaging may further refine noninvasive staging in the future, although current evidence supports the continued routine use of chest CT with intravenous contrast along with PET in suspected N2 disease. Further research is critical to better predict the likelihood of R0 resection following induction therapy.

Statement 6: Direct Extension of Tumor in Continuity with Bulky Mediastinal Nodal Disease Should Be Considered Unresectable (CoR IIa, LoE C-limited data)

Determination of resectability in patients with NSCLC and N2 mediastinal lymph node involvement remains among the most challenging and controversial aspects of thoracic oncologic decision making. Among these scenarios, tumors demonstrating direct extension in continuity with bulky mediastinal nodal disease (see also Statement 7) raise particular concern regarding the feasibility of achieving an R0 resection with acceptable perioperative risk.^{23,29} Historically, bulky N2 disease, commonly defined by nodal size, loss of normal tissue planes, or radiographic evidence of invasion into adjacent mediastinal structures has been associated with lower rates of complete (R0) resection and inferior long-term survival.⁶⁸⁻⁷¹

When the primary tumor appears to be contiguous with involved mediastinal nodes, this may reflect extensive locoregional disease with extranodal extension, increasing the likelihood of positive margins despite aggressive surgical techniques. Multiple retrospective series have demonstrated that incomplete (R1 or R2) resection in N2 disease is associated with poor survival outcomes, (see also Statement 1) underscoring the importance of careful patient selection.^{12,13}

The working group recognized that this radiographic description encompasses a heterogeneous group of patients, and that pretreatment imaging alone may overestimate unresectability in select cases.⁷² Advances in induction systemic therapy, specifically platinum-based chemotherapy combined with immunotherapy, have demonstrated significant rates of tumor and nodal downstaging, including eradication of viable tumor in mediastinal lymph nodes in a meaningful proportion of patients.⁷³ As a result, several panelists emphasized that response to induction therapy

may meaningfully alter resectability, even in cases initially perceived as unfavorable.

The 80% level of consensus, as well as the assignment of a Class IIb recommendation with Level C-limited data evidence, reflects this uncertainty. Although direct tumor-nodal continuity with bulky mediastinal disease should generally be considered unresectable at baseline, the consensus acknowledges that such determinations should not be absolute. Patients should be discussed in a multidisciplinary tumor board setting before definitive treatment planning. Restaging following induction chemoimmunotherapy may reveal separation of tissue planes or sufficient regression to permit resection in highly selected patients at experienced centers. However, this paradigm should only be considered when there is a high likelihood of R0 resection and acceptable operative risk, and when alternative nonsurgical strategies are unlikely to provide equivalent disease control.

Statement 7: Multistation N2 Disease With Nodes >3 cm or Invasion to Adjacent Structures Should Be Considered Unresectable (CoR IIa, LoE C-limited data)

N2 NSCLC represents a heterogeneous disease stage resulting in challenges and ambiguity when defining surgical resectability in this subset of stage III patients.⁶⁹ N2 nodal disease ranges from single station occult nodal metastasis to multistation, bulky (>3 cm measured in short axis) nodal involvement with invasion of adjacent structures. Within this category, there is a subgroup of stage III (N2) with discrete N2 nodal disease who may be amenable to surgical resection.⁷⁴

Although the NCCN Clinical Practice Guidelines consider surgical resection in patients with single-station, nonbulky N2 nodal disease, the NCCN does not endorse surgical resection for bulky, multistation N2 disease.⁴⁶ Chemoimmunotherapy is increasingly utilized in the neoadjuvant setting for patients with locally advanced NSCLC, with data suggesting favorable survival in patients with stage III (N2) disease who receive induction chemoimmunotherapy followed by surgical resection compared with those undergoing definitive concurrent chemoradiation and subsequent immunotherapy.⁷⁵ If bulky nodal disease has responded to neoadjuvant therapy and appears to be resectable at restaging, surgery may be considered. This committee concurs that multistation with bulky N2 nodal disease with or without invasion into adjacent structures should be considered unresectable.

Imaging features of N2 nodal metastases, which may suggest nonresectable disease are not well established and subject to variability among thoracic radiologists and thoracic surgeons. Coalescent lymph nodes with ill-defined or irregular margins are features that may indicate unresectable disease. The presence of enhancing tumor arising from an N2 node and unequivocally extending into an adjacent structure on contrast-enhanced CT imaging is

consistent with invasion. However, distortion of the contour of an adjacent structure by a malignant lymph node is not synonymous with invasion, and the surgeon may be able to dissect the lymph node away from surrounding structures with an R0 resection.

Although some of the radiographic features mentioned above can suggest extranodal extension, it can only be established after resection when tumor cells from a lymph node extend beyond the lymph node capsule.⁷⁶ Although extranodal extension does not equate to unresectable disease, there is limited retrospective data in NSCLC that the presence of coalescent lymph nodes and direct invasion are associated with reduced overall survival; these features have high specificity but low sensitivity for pathologic extranodal extension.⁷⁷ As a result, these imaging findings may be particularly important for the radiologist and surgeon to identify.

Statement 8: It Is Recommended That Patients With NSCLC With Clinical or Pathological N2 Disease and Actionable *EGFR* or *ALK* Mutations Receive Targeted Therapy as Opposed to Induction Chemoimmunotherapy (CoR I, LoE B-nonrandomized)

A reduced benefit of checkpoint inhibitor therapy has been observed across *EGFR*- and *ALK*-driven tumors.⁷⁸ Multiple analyses show lower objective response rates and survival with immunotherapy in these driver mutation subsets.^{79,80} Moreover, administration of immunotherapy before tyrosine kinase inhibitor therapy is associated with increased treatment-related pulmonary toxicity, including severe pneumonitis.⁸¹ These findings support avoiding induction immunotherapy in this population. Gene mutation testing, including, at a minimum, testing for *EGFR* and *ALK* driver mutations, should be performed. It is advisable to perform next-generation sequencing on all patients with lung cancer who may be candidates for neoadjuvant therapy.

Actionable *EGFR* and *ALK* alterations define biologically distinct subsets of NSCLC that demonstrate greater clinical benefit from targeted tyrosine kinase inhibitor therapy. Treatment selection for patients with N2 disease must account for molecular profile, expected therapeutic response, and toxicity considerations. In resected *EGFR*-mutated NSCLC, the Adjuvant Diagnosis of Associated Umbrella Research and Assessment trial demonstrated significantly prolonged disease-free survival with adjuvant osimertinib compared with the placebo.⁸² In the adjuvant setting, alectinib has demonstrated improved progression-free survival and overall survival, leading to Food and Drug Administration approval and new standard of care.⁸³ These data support prioritization of targeted therapy when actionable mutations are present.

In the setting of known N2 disease, neoadjuvant therapy is recommended for most patients, but only preliminary data is

available regarding the use of targeted agents in the neoadjuvant setting. Neoadjuvant Adjuvant Diagnosis of Associated Umbrella Research and Assessment randomized (1:1:1) stage II through IIIB *EGFR*-mutated patients to neoadjuvant osimertinib with platinum-based therapy, neoadjuvant osimertinib monotherapy, or placebo plus platinum-based chemotherapy, with adjuvant osimertinib permitted. One-third of enrolled patients had N2 disease. The primary end point of major pathologic response was 25% and 26% in both of the osimertinib groups compared with 2% with chemotherapy alone. Fifty-three percent experienced nodal downstaging when osimertinib was included in the neoadjuvant strategy, compared with 21% with chemotherapy.⁸⁴

In patients with N2 disease, with actionable *EGFR* or *ALK* alterations, targeted therapy with osimertinib or alectinib, respectively, is now standard of care for adjuvant treatment.^{46,84} For patients with resectable N2 disease and *EGFR* or *ALK* alterations, targeted therapy aligns systemic treatment with tumor biology, offering improved disease control and a more favorable safety profile. In contrast, induction chemoimmunotherapy offers these patients limited expected benefits and increases risk of immune-mediated toxicity and complications during subsequent tyrosine kinase inhibitor therapy. Molecular testing should therefore be incorporated early in the treatment pathway to guide systemic therapy decisions; enrollment in perioperative targeted therapy trials is recommended.

This recommendation is Class I, Level B-nonrandomized for stronger consideration of targeted therapies within the treatment plan rather than immunotherapy, because evidence consistently demonstrates superior outcomes with targeted therapy and diminished benefit from immunotherapy among patients with *EGFR* or *ALK* alterations. While randomized data specific to the neoadjuvant N2 setting remains limited, the consistency of clinical outcomes across disease stages and treatment contexts supports incorporation of targeted therapy rather than immunotherapy in this population.

Statement 9: The Degree of Benefit Derived From Adjuvant Immunotherapy in Patients Who Have Received Neoadjuvant Chemoimmunotherapy Is Unclear. Omission of Adjuvant Immunotherapy may Be Considered in Patients With pCR, Especially in Those Who Have Had Complications From Such Treatment in the Neoadjuvant Setting (CoR IIb, LoE B-nonrandomized)

The contribution of adjuvant immunotherapy after neoadjuvant chemoimmunotherapy and surgery is not fully understood. In numerous clinical trials, pCR was achieved in 17% to 37% of patients.^{5,6,8,24,85} The 5-year EFS in patients who achieved a pCR from 3 cycles of chemoimmunotherapy in CheckMate 816 was 95.3%—nearly all patients who achieved pCR did not experience disease recurrence. Similar

EFS rates were reported in those with a pCR in the KEYNOTE-671, CheckMate77T, and the Perioperative Toripalimab Plus Chemotherapy for Patients With Resectable Non–Small Cell Lung Cancer⁸⁶ clinical trials.^{5,6,24,86} Therefore, as no conclusive evidence has been presented to demonstrate an incremental benefit of adjuvant immunotherapy in patients who have achieved pCR after chemoimmunotherapy, omitting adjuvant immunotherapy may be considered in these patients, particularly those who have experienced immunotherapy-related adverse events.

To further examine this question, a propensity-weighted comparison of 3 cycles of neoadjuvant chemoimmunotherapy with CheckMate 816 and CheckMate 77T was presented at the World Conference on Lung Cancer in 2024. There was no statistically significant difference in EFS between preoperative and perioperative immunotherapy in patients achieving a pCR (HR, 0.58; 95% CI, 0.14–2.40).⁸⁷ Additionally, there was a significant selection bias because only patients receiving at least 1 cycle of adjuvant immunotherapy (142 out of 229 [62%]) were included in the perioperative arm, and likely reflected the “better” performing patients. Therefore, in those patients with pCR, adjuvant immunotherapy can potentially be omitted. The Incorporating Pathologic Response in Patients with Early Stage Lung Cancer to Optimize Immunotherapy in the Adjuvant Setting⁸⁸ randomized trial will attempt to answer this question in a prospective fashion, in which patients with pCR following neoadjuvant chemoimmunotherapy are randomized to receive adjuvant immunotherapy or observation.⁸⁸ The European Thoracic Oncology Platform - Assessing the value of the adJuvant cOmponent of Perioperative chemoimmunotherapy with durvalumab on disease-free survival in resectable NSCLC-lung Phase 3 trial will attempt to answer this question in patients without pCR. Stage IIB through IIIB NSCLC patients who received neoadjuvant chemotherapy and durvalumab without pCR will be randomized to 1 year of adjuvant durvalumab or placebo.⁸⁹

Statement 10: Routine Pathologic Restaging Should not Be Performed Unless There Is a Concern for the Presence of New N3 or M1 Disease (CoR III, LoE C-expert opinion)

Routine pathologic restaging; that is, systematic re-biopsy of mediastinal lymph nodes or distant sites, after neoadjuvant therapy in resectable NSCLC is not generally required, except when imaging or clinical findings suggest new N3 nodal disease or M1 involvement.⁹⁰ Posttreatment re-staging should include routine imaging (CT and/or PET-CT) for response assessment, but tissue confirmation only when new high-risk findings that would preclude curative intent surgery appear.^{66,91} Persistence of nodal disease, as long as it is resectable, should not preclude curative intent surgery.

Persistent or worsening adenopathy or PET positivity may represent fibrosis or post-treatment pseudo-progression,

rather than viable tumor, and pathologic restaging may delay surgery without altering management.⁹² When imaging raises suspicion for N3 involvement or new metastases, obtaining tissue confirmation is important to avoid noncurative surgery or to alter strategy to definitive systemic therapy or radiation. Hence, the most pragmatic approach is not to conduct routine pathologic restaging unless there is concern for N3 or M1 disease, at which point tissue confirmation should be obtained.

Statement 11: For Medically Operable Patients With Resectable N2 NSCLC, the Rates of Treatment-Related Adverse Events During Neoadjuvant Treatment With Chemo-Immunotherapy Are Low, and the Majority of Patients Undergo Surgical Resection Without Significant Delay (CoR I, LoE B-nonrandomized)

In prospective randomized controlled trials, the rates of treatment-related adverse events for patients who received induction chemo-immunotherapy were low and not inferior to patients who received induction chemotherapy alone. In most of the prospective trials, surgery was recommended 4 to 6 weeks after completion of neoadjuvant chemoimmunotherapy. Many choose to perform repeat imaging 3 to 4 weeks after the last cycle of chemoimmunotherapy. Neoadjuvant and perioperative immunotherapy trials that have reported surgical outcomes are shown in Table 2, listing attrition rates and other relevant surgical and oncologic outcomes. In CheckMate 816, grade 3 or 4 treatment related events were 33.5% in the nivolumab group versus 36.9% in the chemotherapy alone. A total of 83.2% of patients underwent surgery in the nivolumab group versus 75.4% in

the chemotherapy alone group. Grade 3 or 4 surgery related adverse events occurred in 11.4% of the nivolumab group versus 14.8% of the chemotherapy alone group; more granular surgical data has been presented in abstract form but not yet published for this trial.⁵ In KEYNOTE-671, grade 3 to 5 treatment-related adverse events occurred in 44.9% of the pembrolizumab group versus 37.3% of the chemotherapy alone group. Treatment-related adverse events led to discontinuation of all trial treatments in 12.6% of the pembrolizumab group versus 5.3% in the chemotherapy alone group. In the pembrolizumab group, 82.1% of patients underwent surgery versus 79.4% for the chemotherapy alone group.²⁴ In the AEGAEN study, 80.6% of the durvalumab group underwent surgery versus 80.7% of the chemotherapy alone group.⁶ In CheckMate 77T, treatment-related adverse events grade 3 or 4 occurred in 32.5% of the nivolumab group versus 25.2% of the chemotherapy-alone group. Nonetheless, definitive surgery was performed in 77.7% of the nivolumab group versus 76.7% of the chemotherapy alone group.⁸ The predominant etiology for the cancellation of surgery in these trials was disease progression, not treatment-related adverse events.

There has been concern that 20% to 25% of potentially resectable patients ultimately do not undergo surgery. In a recent real-world analysis, this rate may be as high as 35%.^{99,100} Not all studies provide detailed information about reasons for surgery cancellation, which were often listed as “Other.” The most common reason for cancellation is disease progression, with only 1% to 2% of cancellations stemming from complications of systemic therapy. Some people directed towards a neoadjuvant pathway are

TABLE 2. Comparison of surgical outcomes in neoadjuvant chemoimmunotherapy trials for non-small cell lung cancer

Trial	Neoadjuvant strategy	n	Resection rate	Participants who are N2+	Approach (%)			Duration (min); frequency of reported surgical difficulty	Type of resection (%)			Mortality (%)			Clavien-Dindo complications≥ 3 (%)
					MIS	Converted	Thoracotomy		Lobectomy (%)	Pneumorectomy (%)	R0 resection (%)	LOS (d)	30 d	90 d	
NADIM 2021 ⁹³	3 cycles platinum + nivolumab	41	41/46 (89)	30/41 (73)	41	10	49	195	78	7	100	5	0%	0	2.4
NEOSTAR 2024 ⁹⁴	3 cycles platinum + nivolumab + ipilimumab	42	42/44 (95%)	NR	12	NR	88	152; 52%	83	7	93	3.75	0	0	19.0
AEGEAN 2025 ⁹⁵	4 cycles platinum + durvalumab	366	284/366 (78)	133/284 (47)	49	NR	49	210	88	9	95	NR	1.4	4.6	6.1
CHIO3 2026 ⁹⁶	4 cycles platinum + durvalumab	30	30/37 (81)	30/30 (100)	63	7	30	47%	93	7	93	3.5	0	0	6.7
KEYNOTE-671 2026 ⁹⁷	4 cycles platinum + pembrolizumab	397	325/397 (82)	168/325 (52)	NR	NR	NR	NR	79	11	92	8	1.8	4	NR
Checkmate 77T N2+ subset 2026 ⁹⁸	3 cycles platinum + nivolumab	91	70/91 (77)	91/91 (100)	26	4	70	213	84	1	86	9	0	NR	NR

Values are presented as n/N (%) unless otherwise noted. LOS, Length of stay; NR, not reported.

aspirationally resectable and at restaging, surgery is not a realistic option, and perhaps never was. It is worth remembering that similar attrition rates occurred in N2 patients in the era of neoadjuvant chemoradiation, ranging between 15% to 35% in several major trials.^{4,101,102}

Statement 12: Surgical Resection Can Be Performed Safely After Neoadjuvant Chemo-Immunotherapy in Patients With Resectable N2 NSCLC, With Low Rates of Pneumonectomy and High Rates of R0 Resection (CoR IIa, LoE B-nonrandomized)

The safety of surgical resection after induction therapy may be measured with numerous indices, including surgical morbidity, as well as lobectomy to pneumonectomy ratio, R0 resection rate, and rate of conversion from minimally invasive to open surgery. The presence of N2 disease, or persistent N2 disease, does not mandate pneumonectomy. In reviewing the completed, prospective, randomized, controlled trials comparing induction chemo-immunotherapy to chemotherapy alone, it was demonstrated that surgical resection after chemo-immunotherapy may be performed safely, with similar or superior surgical outcomes compared to resection after chemotherapy alone (Table 2). In CheckMate 816, the lobectomy to pneumonectomy ratio was 77:17 after chemo-immunotherapy, compared with 61:25 after chemotherapy alone. R0 resection rate was superior after chemo-immunotherapy: 83% versus 78%. Finally, the rate of minimally invasive surgery was superior (30% vs 20%), as was conversion rate from minimally invasive to open surgery (11% vs 16%). CheckMate 77T recently reported surgical results specifically in N2 patients. In the nivolumab group, R0 resection was achieved in 86% of N2 patients and in 84% of non-N2 patients. In the nivolumab group, 1% of N2 patients required pneumonectomy, whereas 14% of N2 patients in the placebo arm required pneumonectomy.⁹⁸

Surgical results of KEYNOTE-671 showed pneumonectomy rates of 11.4% in the pembrolizumab arm versus 12.3% in the placebo arm. Delayed surgery occurred in 4.9% of the pembrolizumab arm versus 7.6% of the placebo arm. Thirty- and 90-day mortality was 1.8% and 4.0% respectively in the pembrolizumab group versus 0.6% and 1.6% in the placebo group. R0 resection was achieved in 92.0% of the pembrolizumab arm versus 84.2% of the placebo arm.⁹⁷

On reviewing surgical data from trials involving preoperative chemoimmunotherapy (Table 2), surgical outcomes have overall been quite favorable, with consistently low pneumonectomy rates (<12%) and high R0 resection rates. It should be noted, that even if pneumonectomy is required, the benefit from neoadjuvant chemoimmunotherapy is as great as seen in the lobectomy group. In CheckMate 816, pneumonectomy patients treated with chemoimmunotherapy had a 5-year overall survival rate of 80% versus 53% in the placebo group.¹⁰³ Both length of stay and use of minimally invasive

TABLE 3. Proposed scoring system to describe severity of fibrosis in the hilum or mediastinum found at operation after neoadjuvant therapy*

Score	Description
0	Normal hilar and mediastinal tissue planes; no fibrosis
1	Mild hilar (1a) or mediastinal (1b) fibrosis not complicating dissection
2	Moderate hilar (2a) or mediastinal (2b) fibrosis creating technically challenging dissection
3	Severe hilar (3a) or mediastinal (3b) fibrosis with obliteration of anatomical planes, precluding resection

*Used with permission from reference.¹⁰³

surgery vary quite a bit by study and by geography. Length of stay has been 3 to 5 days in most trials; 3 trials are reporting length of stay of 7 to 9 days. The use of minimally invasive surgery ranges from 12% to 72%, with conversion to open rates of 5% to 20%. Surgical difficulty is a concern because there may be more hilar fibrosis and perinodal reactive changes related to immunotherapy. Scarring and inflammation resulting from neoadjuvant chemoimmunotherapy can be difficult to predict, and the amount of scarring encountered by the surgeon is difficult to quantitate. Rusch and colleagues¹⁰⁴ have proposed a simple scoring system (Table 3) for grading of surgical difficulty, that if implemented into future trial design, would provide insight into the influence of various neoadjuvant regimens on intraoperative challenges and how they might influence the postoperative course.

Statement 13: For Medically Operable Patients With Resectable N2 NSCLC Disease, and Without Actionable *EGFR* or *ALK* Mutations, Neoadjuvant Chemoimmunotherapy Is Preferred Over Neoadjuvant Chemotherapy, to Optimize Both Pathologic Response and Long-Term Survival (CoR I, LoE A)

Management of patients with resectable N2 NSCLC has evolved substantially with the integration of immune checkpoint inhibitors into perioperative treatment paradigms. Multiple randomized trials have demonstrated that the addition of immunotherapy to platinum-based chemotherapy in the neoadjuvant setting results in superior oncologic outcomes compared with chemotherapy alone, fundamentally altering the standard preoperative approach for patients with NSCLC without actionable *EGFR* mutations or *ALK* rearrangements.

Strong supporting evidence comes from several Phase 3 trials demonstrating that neoadjuvant chemoimmunotherapy improves rates of pCR, EFS, and overall survival when compared with neoadjuvant chemotherapy alone.^{5-8,21,24,58,86,105} Among all patients in these trials receiving

chemoimmunotherapy, EFS is highly predictable, typically 60% to 70% at 2 years, with overall survival at 2 years exceeding 80% in the chemoimmunotherapy arms. These benefits have been observed across clinical stages and programmed death-ligand 1 expression subgroups.⁷³ These trials included patients with cN2 tumors although most did not clarify whether cN2 was single station or multistation, whether nodes were discrete or bulky, and not all required histologic proof of N2 pretreatment. Among trials that do describe single versus multistation N2 disease, there was no obvious difference in outcomes dependent upon those factors. In the NADIM trial, 72% of patients had cN2 disease with 39% of patients having multistation N2 disease.⁵⁸ These patients had a remarkable 24 month-progression-free survival of 67.2% versus 40.9% in the chemotherapy only arm (HR, 0.47; 95% CI, 0.25-0.88) and an overall survival of 85% versus 63.6% (HR, 0.43; 95% CI, 0.19-0.98). In the CheckMate 77T trial, 63.8% of patients had IIIA/B disease and 39.7% of all patients had cN2 disease.⁸ pCR rates were similar for patients receiving nivolumab in those with N2 disease (22.0%) and non-N2 disease (25.5%). Patients with N2 disease specifically had a pCR rate of 22.0% with nivolumab versus 5.6% with placebo, any nodal downstaging of 67% of the nivolumab group versus 59% in the placebo group, downstaging to pN0 in 57% of the nivolumab group versus 44% in the placebo group, and a 1-year EFS rate of 70% with nivolumab versus 45% with placebo (HR, 0.46; 95% CI, 0.30-0.70). Thirty-four percent of patients with N2 had multistation involvement, and no differences in survival were noted in patients with single-station or multistation N2 disease.⁹⁸

The addition of immunotherapy is associated with improved overall survival in these large patient cohorts which included patients with N2 disease. In the recently reported long-term follow-up data from CheckMate 816, among clinical stage IIIA patients (acknowledging that not all of these patients were cN2), 5-year overall survival was 65.3% versus 53.4% favoring chemoimmunotherapy.²¹

The expert panel therefore reached unanimous agreement that for eligible patients without contraindications to immunotherapy or actionable *EGFR* or *ALK* alterations, neoadjuvant chemoimmunotherapy should be favored over chemotherapy alone. In contrast, neoadjuvant chemotherapy without immunotherapy, historically the standard of care, provides only modest survival benefit and inferior pathologic response rates, and therefore should generally be reserved for patients with contraindications to immunotherapy or in whom expected outcomes from the addition of immunotherapy are negligible based on data in the metastatic setting. The panel emphasized that outside of a clinical trial, upfront surgery, neoadjuvant chemotherapy alone, or neoadjuvant chemoradiation is not preferred for medically

operable patients with resectable N2 disease who are candidates for immunotherapy.

DISCUSSION

Management of N2 NSCLC requires a multidisciplinary effort to establish diagnosis, accurately stage, and facilitate complex decision making. These recommendations are primarily directed at surgeons who are navigating treatment strategies in the context of a multidisciplinary team. In this cohort of patients with locally advanced, oncologically challenging lung cancer, treatment has traditionally been neoadjuvant chemotherapy or chemoradiation, followed by surgical resection. Definitive chemoradiation has been employed in patients with unresectable, marginally resectable, or medical inoperable disease. Neoadjuvant chemotherapy combined with immune checkpoint inhibitors has dramatically altered the landscape of care, significantly enhancing resectability, and improving the rate of pCR, disease-free survival, and overall survival in patients undergoing surgical resection.

Some critical principles remain unchanged, including thoracic surgeon involvement early in the evaluation process, thorough pretreatment staging, and the goal of R0 resection. There have been other notable changes in the management of N2 NSCLC: genomic testing, specifically for *EGFR* and *ALK* mutations, is now mandatory before any treatment is rendered because the pathway is significantly different in these patients and expansion of potentially operable populations to include multistation N2 disease and select cases of T4 N2. Alternatively, a hilar tumor confluent with bulky (defined as >3 cm) N2 nodes is generally unresectable, as is disease with bulky and multistation N2 involvement. Defining resectability is difficult, and final determination should lie in the hands of thoracic surgeons focusing on thoracic oncologic surgery, in discussion with a panel of multidisciplinary experts. Restaging testing after neoadjuvant therapy should give clear delineation of the anatomy of the residual disease with contrast-enhanced chest CT and selective use of repeat PET. Routine pathologic mediastinal restaging after induction therapy is not needed, unless there is new concern for N3 or M1 disease. There are now many reports of successful surgical outcomes following chemoimmunotherapy, with reasonably low rates of pneumonectomy (generally <10%), high R0 rates (>90%), and variable but laudable rates of minimally invasive surgery.

Future Directions and Gaps in Knowledge

There are many unanswered questions in the surgical management of N2 NSCLC. As assays of circulating tumor DNA become more sensitive, measurements at various times (pretreatment, posttreatment preoperatively, postoperatively, during and after adjuvant therapy) may result in more personalized and judicious use of systemic therapy.¹⁰⁶

There is great interest in determining when and how systemic therapy can be de-escalated. Should adjuvant therapy be given for 9 to 12 months as in most perioperative trials, or 6 months as in NADIM II, or based on clearance of circulating tumor DNA?

For patients whose tumors harbor driver mutations, there are several active trials (Neoadjuvant and Adjuvant Umbrella Trial-1, Neoadjuvant Adjuvant Diagnosis of Associated Umbrella Research and Assessment, Alectinib in Neoadjuvant Treatment of Stage III NSCLC) that will inform decisions about the use of neoadjuvant tyrosine kinase inhibitors with or without chemotherapy in patients with early stage or with N2 NSCLC.^{84,107} For those without driver mutations, there is emerging data predicting who is more or less likely to respond to immune checkpoint inhibitors, based on mutations such as *KEAP-1*, *STK-11*, *p53*, and variations in tumor micro-environment and gut microbiome.¹⁰⁸

Trials are underway to look at the inclusion of patients with borderline resectable disease to determine who can successfully undergo surgery and what happens to those who cannot. Novel imaging technologies that more effectively inform us about tumor response in conjunction with liquid biopsy will be immensely helpful in better triaging people with lung cancer toward surgery, radiation, or different systemic options.¹⁰⁹

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Conflict of Interest Statement

See [Online Data Supplement](#). Dr Bestvina receives grants and funding from AstraZeneca and BMS; receives personal consulting fees and is on advisory boards for AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Catalyst, Daiichi, EMD Serono, Genentech, Gilead, Guardant, Jazz, J&J, Lilly, Mirati, Novartis, Pfizer, Summit Therapeutics, Tempus, and Turning Point Therapeutics. Dr D'Amico receives consulting fees from Scanlan Instruments. Dr Lanuti receives institutional payments from the National Institutes of Health/National Heart, Lung, and Blood Institute; receives consulting fees from Boston Scientific; and receives honorarium from Medtronic. Dr Liberman receives educational and research grants from Boston Scientific, Olympus, Johnson and Johnson, Intuitive, Merck, Broncus, BMS,

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Key Words: N2 disease, stage III, non-small cell lung carcinoma, neoadjuvant, adjuvant, chemoimmunotherapy, targeted therapy, surgery

APPENDIX E1. SEARCH STRATEGY

N2[tiab] AND (“Carcinoma, Non-Small-Cell Lung”[Mesh] OR ((NSCLC[tiab] OR “Non-small-cell lung” [tiab] OR “non-small cell lung” [tiab]) AND (carcinoma*[tiab] OR cancer*[tiab] OR neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR adenocarcinoma*[tiab] OR carcinogenesis[tiab]))) AND (“stage III” [tiab:~3] OR “stage 3” [tiab:~3] OR “stage three” [tiab:~3] OR “stages III” [tiab:~3] OR “stages 3” [tiab:~3] OR “stages three” [tiab:~3] OR IIIA*[tiab]) AND (treatment*[ti] OR ((“Neoadjuvant Therapy” [Majr] OR neoadjuvant[tiab]) AND resect*[tiab]) OR resect*[ti] OR ((“Chemotherapy, Adjuvant/methods” [Mesh] OR borderline[tiab] OR ((“Thoracic Surgical Procedures” [Mesh] OR resect*[tiab] OR surg*[tiab]) AND (“Methods” [Mesh] OR “methods” [Subheading]))) OR ((“Neoadjuvant Therapy” [Majr] OR neoadjuvant[tiab]) AND (“programmed death-ligand 1” [tiab:~3] OR “programmed death-ligand one” [tiab:~3] OR PDL1[tiab] OR PD-L1[tiab] OR “PD-1 L1” [tiab:~2] OR “PD1 L1” [tiab:~2] OR “Immune Checkpoint Inhibitors” [Mesh] OR immunotherap*[tiab] OR (checkpoint*[tiab] AND inhibitor*[tiab]))) OR ((“Neoadjuvant Therapy” [Majr] OR neoadjuvant[tiab]) AND nodal[tiab]) OR ((“Neoadjuvant Therapy” [Majr] OR neoadjuvant[tiab]) AND R0[tiab]) OR ((“Thoracic Surgical Procedures” [Majr] OR resect*[tiab] OR surg*[ti]) AND nodal[tiab]) OR

((“Thoracic Surgical Procedures” [Mesh] OR resect*[tiab] OR surg*[tiab] OR operat*[tiab]) AND (“Immune Checkpoint Inhibitors” [Mesh] OR immunotherap*[tiab] OR (checkpoint*[tiab] AND inhibitor*[tiab]))) OR ((“Thoracic Surgical Procedures” [Majr] OR resect*[tiab] OR surg*[ti]) AND (“Positron-Emission Tomography” [Majr] OR “Positron Emission Tomography Computed Tomography” [Mesh] OR “PET CT” [tiab] OR “PET Scan” [tiab:~2] OR “PET Scans” [tiab:~2] OR Scan[tiab] OR Scans[tiab] OR PET/CT[tiab] OR PET[ti] OR CT[ti] OR imaging[tiab])) OR ((“Thoracic Surgical Procedures” [Majr] OR resect*[tiab] OR surg*[ti]) AND (“Neoplasm Staging” [Mesh] OR staging[tiab]) AND ((“Neoadjuvant Therapy” [Majr] OR neoadjuvant[tiab]) OR “Immune Checkpoint Inhibitors” [Mesh] OR immunotherap*[tiab] OR (checkpoint*[tiab] AND inhibitor*[tiab]))) OR ((“Neoadjuvant Therapy” [Majr] OR neoadjuvant[ti]) OR ypN2[tiab] OR (“Radiotherapy” [Mesh] OR “radiation therap*” [tiab] OR “radiation therap*” [tiab] OR radiochemo*[tiab]) OR ((resect*[tiab] OR surg*[ti]) AND (“Chemoradiotherapy, Adjuvant” [Majr] OR adjuvant[tiab])))

RESTRICTIONS

AND (2005:2025[pdat]) NOT (casereports[Filter] OR review[Filter] OR systematicreview[Filter])

TABLE E1. Key search concepts and terms*

Key search concept	Key words/terms (free text)	Medical Subject Heading terms (from search strategy)
N2 disease	N2	–
Non–small cell lung cancer	NSCLC; non–small cell lung cancer; nonsmall cell lung cancer; carcinoma; cancer; neoplasm; tumor; tumour; adenocarcinoma	Carcinoma, Non-Small-Cell Lung
Stage III disease	stage III; stage 3; stage three; stages III; stages 3; stages three; IIIA; IIIB; IIIC	Neoplasm Staging
Resectability/surgery	resect*; resection; resections; resectable; surgery; surgical; thoracic surgery	Thoracic Surgical Procedures
Neoadjuvant therapy	neoadjuvant; neoadjuvant treatment	Neoadjuvant Therapy
Adjuvant/multimodal therapy	adjuvant; chemotherapy; chemoradiotherapy; radiotherapy; radiation therapy	Chemotherapy, Adjuvant; Chemoradiotherapy, Adjuvant; Radiotherapy
Immunotherapy/checkpoint inhibitors	immunotherapy; checkpoint inhibitor; checkpoint blocker	Immune Checkpoint Inhibitors
PD-L1/biomarkers	PD-L1; PDL1; programmed death-ligand 1; programmed death-ligand one	–
Imaging/staging	PET/CT; PET; CT; PET scan; CT scan; imaging; scan; scans	Positron-Emission Tomography; Positron Emission Tomography Computed Tomography
Nodal/resection status	nodal; ypN2; R0; borderline resectable	–

*The search strategy incorporated Boolean logic, proximity searching, and truncation to maximize retrieval sensitivity while maintaining specificity and capturing variations in terminology.