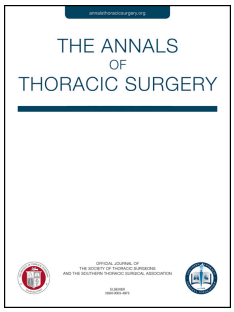

The Society of Thoracic Surgeons Expert Consensus on the Multidisciplinary Management and Resectability of Locally Advanced Non-Small Cell Lung Cancer

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The Society of Thoracic Surgeons Expert Consensus on the Multidisciplinary Management and Resectability of Locally Advanced Non-Small Cell Lung Cancer

Running Head: Resectability and Management Lung Cancer

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The STS Executive Committee approved this document.

EXECUTIVE SUMMARY

The Society of Thoracic Surgeons Workforce on Thoracic Surgery assembled a multidisciplinary expert panel to provide this professional society's perspective on determining resectability and managing locally advanced non-small cell lung cancer (NSCLC) in the context of contemporary evidence. This document was created by generating appropriate questions according to the PICO format (P, population, patients, or problem; I, intervention; C, comparison; O, outcome) to address three major themes: (1) Assessing Resectability and Multidisciplinary Management of Locally Advanced Lung Cancer, (2) Neoadjuvant (including perioperative) therapy, and (3) Adjuvant therapy. Literature evidence was gathered from search engines, and once appropriate statements were generated, a consensus on statements was reached using a modified Delphi method.

Despite the complex decision-making process in managing locally advanced lung cancer, this expert panel agreed on several key recommendations. A multidisciplinary tumor (MDT) board should discuss the patients with locally advanced NSCLC to determine optimal treatment options, and until more data emerge in the future, the surgical resectability should be decided up-front at the time of presentation. In medically operable patients with locally advanced lung cancer without driver mutation (clinical stage II to III), our panel recommends neoadjuvant platinum-based chemotherapy with immunotherapy (neoadjuvant or perioperative) before surgical resection over adjuvant therapy, and the surgical resection should proceed as long as there is no progression of disease after induction treatment. In NSCLC patients with driver mutations, the addition of neoadjuvant immunotherapy to chemotherapy has minimal to no additional efficacy; therefore, patients can be treated with neoadjuvant chemotherapy or chemotherapy with radiation therapy followed by surgical resection and, when approved, adjuvant-targeted therapy. Alternatively, when appropriate, surgery followed by adjuvant targeted therapy (with or without chemotherapy) is an alternative treatment paradigm. The investigation of neoadjuvant targeted therapies is in its early stages, and patients with stage II-III NSCLC (majority adenocarcinoma histology) with driver mutations should be considered for induction treatment only in the context of clinical trials until more data emerges.

Patients with multi-station N2 disease are generally not considered candidates for surgical resection, especially in bulky nodal disease, as they experience poor long-term outcomes. However, surgical resection can be considered in select cases with non-bulky, 2-3 involved N2 stations, particularly if lobectomy is considered likely. Patients with clinical T4 NSCLC (including Pancoast tumor) represent a heterogeneous group. The surgeon must consider the institution's experience and expertise in determining resectability, as achieving complete resection and post-operative management can be challenging. The surgical resection can be considered after induction therapy following MDT discussion at highly experienced centers.

Offering adjuvant immunotherapy after surgical resection for locally advanced lung cancer may be reasonable based on reported perioperative immunotherapy trials, especially in patients with persistent nodal disease after neoadjuvant treatment, although data is unclear on those with pathological complete response(pCR). For EGFR mutant NSCLC, adjuvant osimertinib should be offered for three years (ideally without prior immunotherapy exposure in the neoadjuvant setting). Post-operative radiation therapy (PORT) is not routinely indicated unless the surgical pathology indicates an R1/R2 resection.

ABSTRACT

BACKGROUND: The contemporary management and resectability of locally advanced lung cancer are undergoing significant changes as new data emerge regarding immunotherapy and targeted treatments. The objective of this document is to review the literature and present consensus among a group of multidisciplinary experts to guide the determination of resectability and management of locally advanced non-small cell lung cancer (NSCLC) in the context of contemporary evidence.

METHODS: The Society of Thoracic Surgeon Workforce on Thoracic Surgery assembled a multidisciplinary expert panel comprised of thoracic surgeons and medical and radiation oncologists with established expertise in the management of lung cancer. A focused literature review was performed, and expert consensus statements were developed using a modified Delphi process to address three major themes: (1) Assessing Resectability and Multidisciplinary Management of Locally Advanced Lung Cancer, (2) Neoadjuvant (including peri-operative) therapy, and (3) Adjuvant therapy.

RESULTS: A consensus was reached on 19 recommendations. These consensus statements reflect updated insights on resectability and multidisciplinary management of locally advanced lung cancer based on the latest literature and current clinical experience, mainly focusing on the appropriateness of surgical therapy and emerging data regarding neoadjuvant and adjuvant therapies.

CONCLUSIONS: Despite the complex decision-making process in managing locally advanced lung cancer, this expert panel agreed on several key recommendations. This document provides guidance for thoracic surgeons and other medical professionals in the optimal management of locally advanced lung cancer based on the most updated evidence and literature.

Abbreviations and Acronyms

ALK Anaplastic Lymphoma Kinase

CT Computed Tomography

CPI Check Point Inhibitor

DFS Disease-Free Survival

EFS Event-free survival

EGFR Epidermal Growth Factor Receptor

EHR Electronic Health Record

ERBB2 Erythroblastic oncogene B

FDA Food and Drug Administration

IASLC International Association of Lung Cancer

INT Intergroup Trial

HER2 Human epidermal growth factor receptor 2

MDT Multidisciplinary Tumor-board

MPR Major Pathologic Response

NCCN National Comprehensive Cancer Network

NSCLC Non-small Cell Lung Cancer

NTRK Neurotrophic Tyrosine Receptor Kinase

OS Overall Survival

PCR Pathologic Complete Response

PD-L1 Program Death- Ligand 1

PET Positron Emission Tomography

PFS Progression-Free Survival

PICO. P, population, patients, or problem; I, intervention; C, comparison; O, outcome

PORT Postoperative Radiation Therapy

ROS1 ROS proto-oncogene 1, receptor tyrosine kinase

RET Rearranged during Transfection

RR Response Rate

STS Society of Thoracic Surgeons

SWOG Southwest Oncology Group

TKI Tyrosine Kinase Inhibitor

Lung cancer remains the leading cause of cancer mortality worldwide, with only 18% 5-year survival across all stages.[1] For patients with early-stage (Stage IA/B) non-small cell lung cancer (NSCLC) and select patients with locally advanced (Stage II-IIIA/B) NSCLC, surgery remains a mainstay of treatment.[2] With advancements in systemic medical therapy, radiation therapy, and operative techniques, the role of surgical intervention is rapidly evolving. Increasingly, the optimal management of the patient with locally advanced lung cancer, which includes both surgical and non-surgical therapies, is predicated on an appropriate assessment of "resectability." Therefore, carefully defining resectability takes on the utmost importance.

Obtaining a consensus on what is both possible and appropriate to resect has been challenging due to inconsistent terminology and the lack of standardization of surgical assessment. For example, the terms resectability and operability are often used interchangeably and imprecisely in describing surgical candidacy. Operability is traditionally used to reflect the patient's state of health to tolerate a surgical procedure. On the other hand, resectability typically refers to the anatomic feasibility of achieving microscopically negative margins or an R0 resection.[3] Conventional resectability criteria focus solely on the anatomical tumor extent, but biological factors relevant to prognosis and effectiveness of alternative treatments are increasingly important as personalized treatments using various tumor markers are rapidly integrated into routine clinical practice.[4] As a result, we propose to redefine the term "resectability" to include not only the technical ability to achieve R0 resection but also many biological factors relevant to prognosis, the short and long-term risks of the operation, and the effectiveness of alternative treatments that do not include surgery– in other words, the *appropriateness* of surgical therapy as part of overall patient's treatment.

This document aims to present a consensus among expert members of the Society of Thoracic Surgeons (STS), with input from experts in allied disciplines, to guide the determination of the resectability of locally advanced NSCLC in the context of contemporary evidence.

METHODS

ASSEMBLY OF A WRITING GROUP OF EXPERTS

The STS Workforce on General Thoracic Surgery assembled a national multidisciplinary writing group consisting of 6 thoracic surgeons, 2 medical oncologists, and 2 radiation oncologists with expertise in lung cancer treatment and evidence-based medicine. A task force chair was appointed (S.K.). All members completed the conflict of interest disclosures before embarking on committee work. The STS Quality and Research Council Operating Board reviewed and provided feedback on the expert consensus document and recommendations.

FORMULATION OF OBJECTIVES AND CLINICAL QUESTIONS

Several meetings were held to discuss and develop themes, concepts, and organizational frameworks. This resulted in the creation of subgroups to address 3 major themes: (1) Assessing Resectability and Multi-Disciplinary Management of Locally Advanced Lung Cancer, (2) Neoadjuvant (including peri-operative) therapy, and (3) Adjuvant therapy. The subgroups met several times to formulate questions according to the PICO format (P, population, patients, or problem; I, intervention; C, comparison; O, outcome). These questions were reviewed by the entire group and were refined to produce a finalized list of focused clinical questions. These questions were returned to the subgroups for literature review and evidence synthesis.

LITERATURE REVIEW AND EVIDENCE SYNTHESIS

Literature searches were performed using PubMed and Google search engines for each PICO question from 2002 to the present, limiting studies to the English language. Searches were conducted on a continuous updating basis between July 1, 2023, and February 1, 2024. The task force chair screened the titles and abstracts of the search results for relevance. 154 papers relevant to the PICO questions were identified. Additional papers were added to the body of literature by the group members. The members of

each subgroup reviewed these articles in full text and extracted and synthesized data to formulate a series of evidence-based recommendations. Table 1 summarizes some of the major trials referenced in the recommendations. Each statement was critically examined and revised by the entire group.

DEVELOPMENT OF EXPERT CONSENSUS

The entire expert consensus panel was then asked to evaluate each statement on a 5-point Likert scale. Using the modified Delphi method,[5] 100 % participation was required to achieve an 80% consensus rate ("agree" or "strongly agree"). A second or third round of voting after proper revision was utilized if the threshold was not achieved. Once the consensus statements were accepted, each expert member from the subgroups contributed substantially to writing sections. The document was then re-reviewed by the group, finalized, and sent to the STS Workforce on Evidence-Based Surgery for final approval.

RESULTS

Section 1: Assessing Surgical Resectability and Management of Locally Advanced Lung Cancer

A) The role of the multidisciplinary tumor board (MDT)

- Patients with locally advanced NSCLC (clinical stage IIA-III) should be discussed by an MDT, including but not limited to board-certified thoracic surgeons experienced in lung cancer surgery and thoracic-focused medical and radiation oncologists to discuss optimal treatment options, including a determination of feasibility and appropriateness of resection, potential induction therapies, and alternative treatment options.

- Surgical resectability should be decided up-front. Until more data emerge, patients who are deemed unresectable at the outset should not be given neoadjuvant therapy in an attempt to convert unresectable to resectable disease**.**

In the current landscape of lung cancer treatment, the integration of MDT discussions, particularly for patients with locally advanced NSCLC (clinical stage IIA-III), is pivotal. The complexity of treatment options, bolstered by the U.S. Food and Drug Administration's (FDA) approval of neoadjuvant, peri-operative (CheckMate-816 and KEYNOTE-671, respectively),[6-7] and adjuvant (IMpower010 and KEYNOTE-091)[8-9] immunotherapy and targeted adjuvant therapy (ADAURA and ALINA)[10-11] regimens, necessitates collaborative decision-making. There is high lung cancer treatment guideline adherence for patients presented in an MDT, with over 90% adherence to the standard of care and guideline-concordant algorithms,[12] while non-concordant care is very common outside of this setting.[13] The decision regarding resectability is discussed in MDT, but the final decision on resectability is the responsibility of the thoracic surgeon(s). The treatment algorithm should be an intention-to-treat approach. Patients who are deemed initially unresectable disease should not be treated with neoadjuvant therapy in an attempt to render it resectable. This will only serve to delay or compromise definitive non-surgical therapy. Early investigations are underway to provide more insight into the question of whether conversion to resectability is feasible for those with borderline status based on the tumor's pre-treatment status.[14] However, this approach remains exploratory and should only be attempted in the context of a clinical trial.

The advent of telehealth and virtual and hybrid (combined in-person and virtual) MDTs offers opportunities for improving access to multidisciplinary care, particularly in the post-pandemic era. These platforms facilitate broader participation and ensure continuity in the evaluation and management of complex patients, democratizing access to expert, evidenced-based opinions, and therapeutic clinical trials. This shift towards hybrid or completely virtual MDT meetings not only addresses logistical barriers but also supports equitable patient care by extending specialized consultation to remote and underserved regions.[15-16]

B) Multi-disciplinary management of clinical T2b/T3 N0 NSCLC

- In medically operable patients with 4-7cm NSCLC without clinical nodal metastasis and without a driver mutation, neoadjuvant platinum-based chemotherapy with immunotherapy prior to surgical resection is preferred over adjuvant therapy, particularly in tumors with elevated PD-L1 expression; the data is less clear in 4-5cm tumors whether neoadjuvant chemoimmunotherapy is superior to adjuvant therapy.

The 5-year survival rate for patients with resected NSCLC > 4 cm and pathological N0 is only 59%.[17] Systemic therapy is traditionally recommended as it has been shown to improve overall survival (OS).[18] The recommendation for systemic treatment is even more compelling based on the impressive survival benefits of adding immunotherapy to traditional chemotherapy regimens in recent studies. However, there is still a lack of consensus about whether systemic treatment should be given before or after surgical intervention, as there are no studies directly comparing neoadjuvant to adjuvant chemoimmunotherapy. Therefore, the decisions regarding which approach to take must be informed by the interpretation of available evidence and each approach's potential advantages/disadvantages at the point of care. Updated data from Checkmate-816 and a recently published meta-analysis demonstrates that event-free survival (EFS) and OS are improved, respectively,[19-20] with neoadjuvant chemoimmunotherapy compared to neoadjuvant platinum-based chemotherapy alone in stage II-IIIA patients with PDL>1%; however, the major driver of this effect is likely the stage IIIA patients. Thus, this provides a rationale for offering neoadjuvant chemoimmunotherapy. In addition, published data have shown patients with clinically node-negative 5-7cm NSCLC treated with neoadjuvant chemoimmunotherapy compared to neoadjuvant platinum-based chemotherapy have higher tumor pathologic complete response (pCR) and major pathologic response (MPR) rates,[6] which may translate into long-term OS benefits. The nature of the smaller T2BN0/T3N0 patient subgroups and the appearance of the survival curves suggest that a longer time horizon is required to determine if the neoadjuvant approach is advantageous in these patients.

When considering the evidence in support of adjuvant chemoimmunotherapy, it is important to consider that the 2 existing major trials do not represent chemoimmunotherapy but rather sequential therapy with 1 to 4 cycles of platinum-based chemotherapy followed by 1 year of immunotherapy as monotherapy. Both the IMPOWER-010 and PEARLS/KEYNOTE-091 trials required completion of at least 1 cycle of platinum-based chemotherapy prior to randomizing patients to immunotherapy or placebo.[8-9] It is unclear if outcomes from these studies can be compared to neoadjuvant trials where all eligible patients were randomized and then underwent concurrent chemoimmunotherapy. The adjuvant trials have a potential selection bias that automatically favors the appearance of superior outcomes of adjuvant immunotherapy. Thus, it seems more likely than not that the neoadjuvant approaches are optimal based on observing similar outcomes between the two approaches while being exposed to less selection bias.

From a logistical perspective, a neoadjuvant approach allows for a higher receipt of therapy. In IMPOWER-010 and PEARLS/KEYNOTE-091, the adjuvant therapy trials, only 65% and 52% of patients completed therapy, respectively, compared to 94% and 100% of patients in Checkmate-816 and NADIM trials.[6,8-9,21] This finding has been replicated in comparisons of neoadjuvant versus adjuvant therapy both in lung cancer and other cancer sites (e.g., esophageal cancer).[22] Some of this effect is likely related to the fitness of patients to tolerate systemic therapies after surgery or patients' preference or higher tolerance for a shorter course of neoadjuvant therapy (3-4 months) compared to a 1-year-long immunotherapy regimen after several months of cytotoxic chemotherapy.

On the other hand, a major criticism against the neoadjuvant approach for these patients with early-stage disease is that it may prevent them from getting the most important component of their curative therapy, which is surgery. In the published neoadjuvant/peri-operative chemoimmunotherapy trials, up to 20% of patients do not reach planned surgery due to adverse events; however, most of these patients are not those in the T2b/T3N0 group.[6-7]

Finally, neoadjuvant therapy has theoretical benefits related to the antigen-priming effects of receiving immunotherapy while the tumor is in situ.[23] Although preclinical and mechanistic studies

speculate potential benefits, no randomized or controlled trials demonstrate that this translates to clinically meaningful improvements in survival.

C) Multi-disciplinary management of clinical T1-3 N1 NSCLC

- In medically operable patients with clinically involved single or multiple N1 nodes without driver mutations, neoadjuvant platinum-based chemotherapy with immunotherapy prior to surgery is preferred over adjuvant therapy, particularly in tumors with elevated PD-L1 expression.

In selected patients with NSCLC with N1 involvement and lacking a driver mutation, neoadjuvant chemoimmunotherapy is likely to provide greater oncologic benefit than adjuvant sequential chemoimmunotherapy. However, there is no randomized study directly comparing the two approaches. The subgroup analyses of KEYNOTE-671 show similarly impressive EFS and, ultimately, OS for patients with stage II and stage III disease compared to historical controls.[7] It must be noted, however, that the confidence intervals for the hazard ratio for event-free survival for patients with stage II barely reach across 1.

The case for induction chemoimmunotherapy is even more compelling for patients with tumors with elevated PD-L1 expression, as higher PD-L1 expression correlates with greater response rates. For example, in NADIM, the PD-L1% was predictive of pathological response, with an area under the curve of 0.785 for PD-L1% to distinguish MPR from incomplete pathological response. A PD-L1% $\geq$ 25 predicted MPR with 65% sensitivity and 100% specificity.[21]

Finally, a substantial number of patients with clinical N1 disease will, in fact, prove to have pathological N2 disease, and the recommendation for induction chemoimmunotherapy is stronger in N2 disease.[24] Furthermore, the involvement of a single N1 lymph node is likely different than

that of multiple N1 lymph nodes, with multiple involvement behaving more like N2 disease and thus with a stronger likely benefit from induction over adjuvant therapy.

D) Multi-disciplinary management of clinical T1-3 Single Station N2 NSCLC

- In medically operable patients with biopsy-proven NSCLC with single-station, non-bulky N2 disease without driver mutations, surgical resection is generally appropriate as part of a multimodality approach**,** and neoadjuvant platinum-based chemotherapy with immunotherapy prior to surgery is preferred over adjuvant therapy.

- In patients with NSCLC with pathologically proven single-station**,** bulky N2 disease, there is not enough data currently to guide whether surgical resection is superior to other treatment options. However, in select cases, particularly if lobectomy is considered likely, surgery may be considered as a part of multimodality therapy after MDT discussion. Inclusion of these patients in clinical trials is strongly encouraged.

The optimal management of patients with clinical N2 disease remains unclear, with the role of surgical resection debated against other treatment options in the past due to poor long-term survival and high risk of distant metastasis. In several phase III randomized trials comparing induction chemotherapy/chemoradiation treatment followed by surgery to definitive chemoradiation treatment, there was no difference in overall survival.[25-26] However, in the INT0139 study, the progression-free survival was significantly better in the surgical arm.[27] Moreover, in a subgroup analysis, patients undergoing lobectomy had a better outcome than did a matched population treated by radiotherapy. In multiple retrospective and meta-analysis studies, particularly in the setting of single-station nodal disease, the outcomes of surgical intervention in non-bulky single-station N2 disease appear to be favorable.[28-29] With encouraging recent findings from systemic chemotherapy with immunotherapy demonstrating

significant improvement in OS and progression-free survival (PFS),[6-7] it is reasonable to offer surgical resection, particularly lobectomy, as a primary local therapy as long as there is no tumor progression on induction treatment. Induction therapy is generally recommended, as opposed to adjuvant therapy, as several studies have shown tumor regression, improved R0 resection, and low surgical attrition rates with neoadjuvant compared to adjuvant therapy, although this remains unexplored in a head-to-head trial.[7]

We define bulky mediastinal lymphadenopathy as lymph nodes ≥ 2.5cm in short-axis diameter on CT imaging or those showing extranodal involvement or groupings of multiple smaller lymph nodes.[30] The radiographic findings of mediastinal infiltration with encasement of hilar vessels and airways preventing differentiation or measurement of discrete lymph nodes also fall into this category, according to the American College of Chest Physicians.[31] Retrospective series have shown that patients with NSCLC and bulky N2 disease experience worse long-term cancer-specific outcomes when compared to patients with non-bulky lymph nodes.[30-32] However, there is no data directly comparing outcomes between surgery and other treatment modalities in this group of patients. Pathological downstaging after neoadjuvant therapy has been associated with improved long-term cancer-specific outcomes in patients with N2 disease.[33] In light of higher response rates (i.e., major pathological response and complete pathological response) with the use of newer neoadjuvant therapy regimens combining a platinum doublet with an immune checkpoint inhibitor,[14-15] it is reasonable to offer multimodality therapy to a highly select group of patients with single station bulky N2 disease after MDT discussion. This is particularly true if surgery, as part of multimodality therapy, would involve a lobectomy, as this is associated with better perioperative outcomes and long-term survival when compared to pneumonectomy.[27] Due to the lack of data on the long-term outcomes of these patients with surgery versus other treatment modalities, inclusion in clinical trials is strongly recommended and should be discussed with the patient if a trial is available.

E) Multi-disciplinary management of multi-station (≥2) N2 NSCLC

- Patients with NSCLC with pathologically proven multi-station N2 disease are generally not considered candidates for surgical resection as they experience poor long-term outcomes after surgery, especially in bulky nodal disease. However, in select cases with non-bulky, 2-3 involved N2 stations, particularly if lobectomy is considered likely, surgery might be considered as a part of multimodality therapy after MDT discussion. Inclusion of these patients in clinical trials is strongly encouraged.

Multi-station N2 involvement has been consistently demonstrated to be associated with worse long-term cancer-specific outcomes after surgery as part of a multimodality therapy strategy.[29-30] As such, the IASLC proposes a new N descriptor as part of the 9th edition of the TNM classification system, separating N2 disease into single (N2a) and multiple stations (N2b) to better reflect the differences in long-term survival.[34] In combination with the presence of bulky N2 disease, outcomes are expected to be worse. In a survey of 21 National Comprehensive Cancer Network (NCCN) member institutions in 2010, only 16.7% would consider surgery in patients with multi-station N2 disease with bulky lymph nodes.[35] Therefore, these patients are widely considered to have unresectable disease and should be referred for consideration of alternative non-surgical treatment. In patients with non-bulky multi-station N2 disease, 47.6 % of the NCCN institutions would consider surgery. In highly selected patients (e.g., patients with high PDL-1 scores and only 2-3 involved N2 stations), surgery might be considered as a part of multimodality therapy after the MDT discussion. Inclusion of these patients in clinical trials is strongly encouraged and should be discussed with the patient if a trial is available.

F) Multi-disciplinary management of persistent N2 nodes after induction therapy and surgical resection

- For patients with resectable NSCLC and persistent N2 disease after induction therapy but without progression, it is generally appropriate to proceed with surgical resection.

Patients with NSCLC and N2 disease deemed resectable at MDT who undergo multimodality therapy must undergo re-staging after receiving neoadjuvant therapy. Re-staging must include at least a chest CT scan and/or PET/CT scan. These imaging studies intend to rule out disease progression. If there is no radiographic progression (i.e., any response or stable disease), then proceeding with surgical resection is indicated. Certainly, response to neoadjuvant therapy has been associated with favorable long-term cancer-specific outcomes in patients with NSCLC and N2 disease who undergo multimodality therapy. In particular, pathological downstaging or mediastinal clearance (i.e., ypN0-1) has been associated with improved OS and PFS.[27,33] Invasive mediastinal re-staging is not routinely indicated without suspected disease progression on imaging. Phase III randomized clinical trials studying multimodality therapy, including surgery, in patients with NSCLC and N2 disease have not mandated invasive mediastinal re-staging in their protocols and only excluded patients in the event of disease progression after neoadjuvant therapy.[6-7,26-27]

G) Multi-disciplinary management of T4 disease

- Patients with clinical T4 NSCLC represent a heterogeneous group of patients, and in selected patients with T4 N0-1 disease, surgical resection can be considered after induction therapy following MDT discussion at highly experienced centers. Clinical examples include:
    - Patients with NSCLC > 7 cm or satellite nodules in different lobes with N0 or N1 involvement
    - Patients with T4 N0-1 tumors invading the diaphragm, mediastinal structures, recurrent laryngeal nerve, vertebral body, or carina

- Patients with T4N2 tumors are generally considered poor candidates for surgery for curative intent and are ideally treated with non-surgical therapies.

Clinical T4 lung cancer represents a heterogeneous group of diseases defined by tumor size, tumor invasion into mediastinal structures, as well as the diaphragm and vertebral bodies, and metastasis to separate ipsilateral lobes.[36] Over the years, the role of surgical resection has been debated and studied, with the surgical and oncologic outcomes being highly variable on the institutional expertise to achieve R0 resection and clinical factors such as N2-N3 involvement, which portend poor prognosis.[37-38] Therefore, surgical intervention is not generally recommended in patients with T4N2-3 disease outside of a clinical trial. However, recent data suggests that surgery as part of multimodality therapy may confer a survival benefit compared to chemoradiation alone in a subset of patients with T4N2 NSCLC presenting as a small primary tumor (≤3cm) with additional ipsilateral nodules.[39]

Surgery for T4 NSCLC appears effective in highly selected patients without N2 involvement and where an R0 resection can be achieved, with reported 5-year overall OS ranging from 30-60%.[40-41] There is no randomized study comparing surgical intervention with that of definitive chemoradiotherapy for operable T4 N0-1 NSCLC. Considering the 5-year survival of only 15% for patients with pathologic T4 N0-1 M0 NSCLC who received chemoradiotherapy in a subgroup analysis of the Southwest Oncology Group (SWOG) phase II 9019 study,[42] surgical interventions for curative intent should be considered if possible. However, surgical approaches must be balanced against the possibility of R1 resection and treatment-associated morbidity. Therefore, thorough mediastinal staging and robust discussion in the MDT are a must before undertaking surgery on these patients.

It is unclear whether the prognosis is affected by the subtype of T4 tumor. While some literature demonstrated no difference in patient survival among T4 subtypes,[40] more recent studies have indicated that patients with T4 involvement by satellite nodules and involvement of pulmonary great vessels had a lower risk of death compared to patients with tumor extension into other mediastinal structures or tumor > 7cm.[41,43] The surgical resection of other sites, including the vena cava, vertebral body, diaphragm, mediastinum, limited atrium, and carina, is technically feasible and with reasonable patient survival outcomes;[44-45] therefore, surgical resection can be pursued if R0 resection is anticipated. The surgical

resection of the T4 tumors involving the aorta or esophagus has also been described in the literature but is associated with high morbidity and poor prognosis;[46] therefore, surgical consideration should be made with extreme caution, if not altogether avoided.

As CHECKMATE-816 demonstrated significant tumor regression, major pathological response, and improved R0 resection with induction chemotherapy and immunotherapy,[6] induction chemotherapy and immunotherapy for patients with T4 disease, especially in tumors with N1 involvement and elevated PD-1 levels can be considered. For patients with tumors with driver mutations or involving the vertebral body or some cases of chest wall (T3) where adequate resection margins are of a concern, neoadjuvant chemoradiation may be employed to optimize the probability of an R0 resection as retrospective single-institutional data and prospective single-arm Phase II studies (e.g., CJLSG0801) offer the best available data for optimal management of patients with chest wall and/or vertebral body invasion.[47-48]

H) Multi-disciplinary management of Superior Sulcus (Pancoast) Tumor

- For patients with resectable Pancoast tumors without N2 node involvement, pre-operative concurrent chemoradiation followed by surgery remains the standard treatment over induction chemotherapy with immunotherapy, outside of clinical trials.

Superior sulcus tumors represent a challenging group of NSCLC. Currently, induction chemoradiation followed by surgery is the standard treatment in patients without N2 involvement, as the Intergroup trial (INT-0160) of induction doublet chemotherapy with concurrent 45 Gy radiotherapy followed by surgery reported significantly improved 5-year survival, high rates of complete resection, and pCR in both T3 and T4 tumors, 76% and 56%, respectively.[49] These excellent results have led some to speculate about the potentially distinct biology of these malignancies,[50] reinforcing the need for additional biological and biomarker stratification for these tumors.

It is important to note that only patients with N0-N1 disease were included in INT-0160. Outcomes data indicates that patients with N2/N3 disease have a substantially worse prognosis and, therefore, have

not been considered candidates for surgical resection.[51] Other contraindications for surgery include extensive local involvement of the brachial plexus due to poor survival, morbidity, and a high rate of incomplete resection.[52] The resection of the lower parts of the plexus, especially of the C8-T1 roots, has been performed in the surgical treatment of the Pancoast tumor.[53] Loss of the T1 root is well tolerated, but the removal of the C8 or lower trunk of the brachial plexus leads to loss of hand function; therefore, consideration for surgical resection must be tempered with morbidity associated with the procedure. Vertebral body and vascular involvement can be resected with a good prognosis as long as R0 resection can be achieved.[54-55]

The preferred approach for patients with N0/1 disease is the use of neoadjuvant systemic chemotherapy with the addition of concurrent radiation to optimize local control in a site where additional local invasion can lead to significant morbidity. The role of chemotherapy with immunotherapy, although intriguing, remains speculative for these tumors, and further investigations in the future will need to clarify this area.

Section 2: Neoadjuvant therapy

A) Neoadjuvant vs perioperative therapy in resectable NSCLC

- Patients may receive either neoadjuvant or perioperative (peri-adjuvant) chemoimmunotherapy with stage IIA and higher NSCLC. It remains unclear which approach is superior, but the attainment of a pathological complete response after neoadjuvant therapy predicts event-free survival.

There are no studies that directly compare neo-adjuvant to perioperative chemoimmunotherapy; thus, the decisions regarding which approach to take must be informed by the interpretation of available evidence as well as the potential advantages/disadvantages of each approach. It is still unclear if the addition of the post-operative immunotherapy adds any additional survival benefit, although the early reports of the peri-operative KEYNOTE-671 and Checkmate-77T trials show better event-free survival

(EFS) hazard ratios (both 0.58) compared to neoadjuvant Checkmate-816 (0.68).[6-7,56] Whether this translates to a persistent EFS or OS advantage remains to be seen as trial data mature. Other major unanswered questions are whether any potential incremental benefits are worth the potential increase in toxicity, cost, prolonged duration of therapy from a patient's quality of life, and how to select those patients who might benefit from postoperative immunotherapy.

B) The level of PD-L1 and guidance of pre-operative therapy

- In patients with surgically resectable stage II-III NSCLC eligible for neoadjuvant chemoimmunotherapy, tumor PD-L1 expression predicts response to neoadjuvant therapy, but lack of PD-L1 expression should not be used to exclude patients from consideration of neoadjuvant immunotherapy.

Tumor PD-L1 expression is an important predictor of response to anti PD-1/PD-L1 immunotherapy in NSCLC.[57] PD-L1 expression is determined using a variety of validated antibody tests, including 22C3, 28-8, SP263, and SP142, and is categorized based on the percentage of tumor cells that stain positive, with the major division categories of <1% (0%), 1-49%, and 50% or greater.[58] Approximately one-third of lung cancers fall into each of these categories, and expression appears relatively independent of histology and the presence of molecular driver mutations.

The correlation between increasing PD-L1 expression and immunotherapy response appears to apply in the neoadjuvant setting. In early phase II trials using neoadjuvant immunotherapy alone, responses were observed regardless of PD-L1 expression, but the numbers of patients were small, and many patients had tumors with unknown PD-L1 expression status.[59-60] Of the reported phase III trials that incorporate chemotherapy plus immunotherapy, most demonstrate a correlation between increasing PD-L1 expression and pCR. With neoadjuvant nivolumab plus chemotherapy,[6] higher PD-L1 expression correlated with patients' improved disease-free survival (DFS) and tumor pCR rate. Similar trends were noticed with DFS after treating patients with perioperative nivolumab plus chemotherapy.[56] In phase III studies of

perioperative pembrolizumab with chemotherapy, higher PD-L1 expression also correlated with improved patient DFS and OS.[7,61] Using perioperative durvalumab with chemotherapy, a correlation with higher PD-L1 expression and patient DFS was also noted, but this was not statistically significant.[62] However, in all of these trials, there still appears to be a modest benefit from adding immunotherapy to chemotherapy treatment regimens, even in patients with PD-L1 negative tumors. Thus, while it is reasonable to consider PD-L1 expression as one of many factors guiding the decision to use immunotherapy, the absence of PD-L1 expression should not be used to exclude patients from its consideration.

C) Contraindications to induction chemoimmunotherapy.

- In patients with stage II-III NSCLC that is surgically resectable, the addition of neoadjuvant immunotherapy to chemotherapy has minimal to no additional efficacy in tumors with mutations in EGFR, ALK, ROS1, RET, ERBB2 (HER2), and NTRK, leading to a recommendation against use in these molecular subtypes. These patients can be treated with neoadjuvant chemotherapy or chemotherapy with radiation therapy followed by surgical resection and, when approved, adjuvant-targeted therapy. Alternatively, when appropriate, surgery followed by adjuvant targeted therapy (with or without chemotherapy) is an alternative treatment paradigm.

In stage IV metastatic NSCLC, immunotherapy is rarely effective for patients with tumors with driver mutations in EGFR, ALK, ROS1, RET, and ERBB2 (HER2).[63] Additionally, targeted oral therapies, for example, osimertinib for patients with EGFR mutant NSCLC, have increased toxicity risks, including pneumonitis and liver function abnormalities after checkpoint immune therapy administration.[64] While the KEYNOTE-671 and AEGEAN perioperative immunotherapy trials allowed enrollment of patients with EGFR- and ALK-positive NSCLC, very few patients were enrolled. But in these and the CheckMate-816 trial, never-smoking patients -- who represent the majority with tumors bearing these

mutations -- did not have a significant survival benefit with the addition of immunotherapy to chemotherapy.[6-7] Therefore, we do not recommend neoadjuvant or adjuvant immunotherapy for these NSCLC subtypes.

The use of cytotoxic chemotherapy is still strongly encouraged in the neoadjuvant and/or adjuvant settings for patients with stage II-III NSCLC with driver mutations. For patients with EGFR mutant or ALK-positive NSCLC, there are data supporting treatment with adjuvant-targeted tyrosine kinase inhibitor (TKI) therapy. Patients with tumors harboring an EGFR driver mutation treated with osimertinib, given for 3 years after surgery, demonstrated an improved OS, and treating patients with ALK-positive NSCLC with adjuvant alectinib has demonstrated a prolonged DFS.[65-66]

D) The role of induction targeted therapy

- The investigation of neoadjuvant targeted therapies is in its early stages, and patients with stage II-III NSCLC (majority adenocarcinoma histology) with driver mutations should be considered for, and if available undergo active discussion about clinical trials that incorporate appropriate targeted therapies, including neoadjuvant therapy.

Despite the theoretical advantages of neoadjuvant therapy, the evidence for induction therapy using targeted agents remains sparse and inconclusive. Among several small non-randomized neoadjuvant studies with TKI, the largest show impressive response rates (RR) of 55-71%, a major pathologic response (MPR) rate of 24%, and adverse events all ≤ grade 3.[67-68] The only randomized neoadjuvant study tested erlotinib vs. gemcitabine/cisplatin administered to patients both pre and postoperatively, with n=72.[69] The RR was 54% vs 34%, and the MPR rate was 10% vs. 0%, both favoring the patient group treated with erlotinib. The progression-free survival (PFS) was significantly greater in patients treated with erlotinib (22 vs. 11 mo.), but the median OS was ultimately no different (42 vs. 37 mo., p=0.51).

It is possible that since targeted treatments tend to reduce tumor burden rather than completely eliminate tumor cells, their use in the neoadjuvant setting will not prove as effective as chemoimmunotherapy. There is not the same benefit to administering targeted therapies to patients while their tumor/tumor antigens remain in place as there likely is with immunotherapy. Lastly, there is some concern that wound healing in patients treated with EGFR TKIs before surgery may be impaired, although this has not been borne out in the small studies published to date.[70]

Therefore, patients with resectable, locally advanced N0/N1 NSCLC-bearing targetable driver mutations should, outside of clinical trials, undergo either induction chemotherapy followed by resection or primary resection followed by adjuvant targeted therapy with or without chemotherapy. However, the putative advantages of neoadjuvant treatment are sufficiently large that additional clinical trials of induction-targeted therapies should be carried out. Current ongoing neoadjuvant targeted therapy trials include the randomized NeoADAURA trial testing osimertinib and the phase II ALNEO trial testing alectinib.[71-72]

Section 3: Adjuvant therapy

A) The role of adjuvant systemic therapy for patients with persistent nodal disease who received pre-operative induction therapy (i.e., chemoimmunotherapy).

- Although patients with persistent N2 disease after neoadjuvant chemoimmunotherapy have inferior oncologic outcomes, the role of additional adjuvant chemotherapy is unknown. Offering adjuvant immunotherapy to patients may be reasonable based on reported peri-operative immunotherapy trials.

- Adjuvant immunotherapy may be continued if following a perioperative regimen with phase III data, and for EGFR mutant NSCLC, adjuvant osimertinib should be offered for 3 years (ideally without prior immunotherapy exposure in the neoadjuvant setting).

Complete surgical resection, tumor downstaging, and pCR have been validated predictors of long-term patient survival after neoadjuvant therapy in the pre-immunotherapy era. Patients with persistent N2 disease after neoadjuvant chemotherapy generally experience suboptimal survival outcomes, but aggressive local therapy is warranted in appropriate patients.[73] In the phase III peri-operative chemoimmunotherapy trial, Keynote-671, pathologic complete response was noted in 18.1% of patients receiving pembrolizumab and 4.0% of patients receiving placebo, and pembrolizumab significantly improved EFS.[7] An exploratory analysis showed an EFS benefit in the pembrolizumab group regardless of whether participants had an MPR or a pCR. Given these findings and those of other immunotherapy trials, it is appropriate to offer adjuvant immunotherapy in patients with persistent nodal disease.

For patients who are not appropriate for neoadjuvant immunotherapy, such as those patients whose tumors have activating EGFR mutations (del 19/exon 21 L858R) or ALK translocations, neoadjuvant chemotherapy alone is appropriate. A meta-analysis has suggested that cisplatin-based induction chemotherapy before surgery conferred an absolute benefit of 6%, increasing overall survival across all stages of the disease from 14% to 20% at 5 years.[74] With sensitive EGFR mutations, adjuvant osimertinib, given for three years, improves OS (HR 0.49, 95% CI 0.33-0.73) as the previously noted ADAURA trial.[10] For ALK-positive mutation, the ALINA trial (NCT03456076) demonstrated improved DFS in the alectinib group (median DFS NE vs 41.3 months; 24-month DFS rate 63.7% vs 93.6%, HR 0.24; 95% CI: 0.13–0.43), and is now FDA approved, though in practice it is reasonable to consider adjuvant chemotherapy preceding it.[75]

B) The role of postoperative radiation therapy (PORT) after induction therapy (i.e., chemoimmunotherapy).

- In patients with NSCLC with N2 involvement who received neoadjuvant chemotherapy with immunotherapy followed by surgery, PORT is not routinely indicated. If significant persistent mediastinal nodal disease exists (for example, ypN2 > 1 nodal station), a small volume, highly conformal PORT may be considered as an option (versus additional systemic therapy) after MDT discussion. Enrollment in clinical trials is strongly encouraged, and if available, clinical trials should be discussed with the patient.
- PORT should be considered if the surgical pathology indicates an R1/R2 resection.

Currently, there is insufficient evidence to support the routine use of PORT in the treatment of patients with resected pN2 NSCLC who have undergone neoadjuvant chemoimmunotherapy. PORT was not part of the perioperative/adjuvant strategy in the randomized trials of neoadjuvant chemoimmunotherapy vs chemotherapy alone that have been published to date. As such, it was administered only in a minority of patients; for instance, ~8% of patients received PORT ± chemotherapy in CheckMate-816.[6] The historical rationale for PORT was the high rates of locoregional recurrence associated in patients with resected N2 disease(~20-30%) which can be reduced by radiation.[76] Similarly, in the contemporary PORT-C trial randomizing patients with incidental or gross N2 disease to adjuvant chemotherapy vs adjuvant chemotherapy followed by PORT, the 3-year rate of locoregional recurrence rate after adjuvant chemotherapy was 18.3%, which was decreased to 9.5% after PORT.[77] Locoregional recurrence rates after neoadjuvant chemoimmunotherapy ± adjuvant immunotherapy have yet to be firmly established. In the NADIM II trial of neoadjuvant chemoimmunotherapy versus chemotherapy alone for stage IIIA/B NSCLC, 16 out of 53 resected tumors in the experimental arm recurred, with only 6/53 (11.3%) being local recurrences at a relatively short median follow-up time of 26.1 months.[78] No high-level evidence exists that a reduction in locoregional recurrence rates from PORT translates into an OS benefit. However, it is

recognized that in individual patients, local tumor regrowth can be life-threatening, compromise quality of life, or lead to distant metastases.[77,79]

In general, PORT should be considered in uncommon cases of residual postoperative macroscopic or microscopic disease (R2 or R1). The least contentious microscopic residual disease states justifying the use of PORT include positive parenchymal, bronchovascular, and soft-tissue margins. The impact of other factors potentially increasing nodal recurrence risk, such as incomplete lymphadenectomy, significant residual nodal burden with more than one involved mediastinal lymph node (*i.e.*, persistent ypN2), or extracapsular nodal extension, is unclear.[80]

Consideration of PORT in individual patients must consider the well-established associations of PORT with mortality and cardiopulmonary morbidity, as reported in the LungART trial.[79] The use of highly conformal radiation techniques or protons may be associated with lower toxicity rates compared to the more traditional 3D fields prevalent in the LungART trial. Careful attention must also be given to the size/location of radiation target volumes and the sparing of the heart, its substructures, and lungs, especially in the setting of additional adjuvant systemic therapy. Enrollment of patients into clinical trials examining adjuvant therapy strategies is strongly encouraged.

COMMENT

The contemporary management of patients with locally advanced lung cancer is undergoing significant changes as new data are emerging in the context of neoadjuvant and adjuvant immunotherapy and targeted treatments. As such, patients with locally advanced NSCLC should be presented at an MDT to discuss optimal, evidence-based treatments. Complete surgical resection remains the most significant predictor of survival in patients with locally advanced lung cancer, and the term “resectability,” should be understood by all to encompass not only the anticipated ability to achieve R0 resection but also the risks of the anticipated surgery, biological factors relevant to prognosis, and the effectiveness of possible

alternative treatments. Resectability should not mean that we "can" take it out, but rather we "should." Thus, a thoracic surgeon must be knowledgeable in the latest data to be the patient advocate for optimal surgical intervention. Table 2 highlights the consensus summary of the resectability of locally advanced NSCLS based on clinical stages. Accurate preoperative diagnosis, staging, and molecular classification are critical to guide patients and the multidisciplinary team in achieving the best possible care. Based on current data, the combination of neoadjuvant chemotherapy and immunotherapy (with or without additional adjuvant systemic therapy) is preferable for most patients with locally advanced NSCLC, without driver mutations, with N1 or N2 nodal metastasis or large tumors. The role of adjuvant immunotherapy is unclear in patients with resected, persistent nodal disease (i.e., present pre-operatively), although there seem to be potential benefits. Adjuvant radiation therapy must take into account patient-specific factors, including the potential for significant toxicity. A clear indication for PORT exists only in patients with an R1 or greater resection. As it relates to resectability, induction treatments should not be given with the intention of "converting" a non-surgical candidate to a surgical candidate. Finally, surgeons should take responsibility in determining the feasibility of resection, considering the institutional surgical expertise and ability to achieve an R0 resection. Alternative treatments, including systemic treatments and radiation therapy, are likely better than suboptimal surgical resection.

Surgical therapy remains an invaluable part of the multidisciplinary management of locally advanced lung cancer. "Resectability" will continue to evolve as cancer treatments become more personalized based on factors such as predictive biomarkers, circulating DNA, radiographic imaging features, and other currently unknown technological advances. Thoracic surgeons will continue to adapt and play a critical role in patient management and care.

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Table 1. A Summary of Major Trials Referenced in the Consensus Statements.

Trial Name	Author/Year	Intervention Timing	Treatment Type	Study Design	Result
CheckMate-816	Forde, et al.[6] 2022	Neoadjuvant	Immunotherapy/ immune CPI	Phase III trial: Induction nivolumab+chemotherapy vs chemotherapy alone followed by surgical resection.	The neoadjuvant group had longer EFS and MPR.
KEYNOTE-671	Wakelee, et al.[7] 2023	Perioperative	Immunotherapy/ immune CPI	Phase III trial: Induction pembrolizumab+ chemotherapy followed by adjuvant pembrolizumab vs induction chemotherapy followed placebo after surgical resection	The peri-operative pembrolizumab improved EFS, MPR compared to neoadjuvant chemotherapy group.
IMpower010	Felip, et al.[8] 2021	Adjuvant	Immunotherapy/ immune CPI	Phase III trial: Adjuvant chemotherapy followed by atezolizumab vs adjuvant chemotherapy after surgical resection	The adjuvant atezolizumab group had improved DFS compared to adjuvant chemotherapy only group.
PEARLS/KEYNOTE-091	O'Brien, et al.[9] 2022	Adjuvant	Immunotherapy/ immune CPI	Phase III trial: Adjuvant chemotherapy followed by pembrolizumab vs adjuvant chemotherapy after surgical resection	The adjuvant pembrolizumab group had improved DFS compared to adjuvant chemotherapy only group regardless of PD-1 expression.
ADURA	Wu, et al.[10] 2020	Adjuvant	Targeted therapy/ EGFR TKI	Phase III trial: EGFR+ NSCLC received adjuvant osimertinib vs placebo after surgical resection	The adjuvant osimertinib group had improved DFS compared to placebo group.
ALINA	Solomon, et al.[11] 2023	Adjuvant	Targeted therapy/ ALK TKI	Phase III trial: ALK+ NSCLC received adjuvant alectinib vs chemotherapy after surgical resection	The adjuvant alectinib group had improved DFS compared to placebo group.
NADIM II	Provencio, et al.[78] 2023	Perioperative	Immunotherapy/ immune CPI	Phase II trial: Induction nivolumab+chemotherapy followed by adjuvant nivolumab	The peri-operative nivolumab + chemotherapy had improved OS and pCR than chemotherapy alone in patients with resectable stage IIIA NSCLC.
CheckMate-77T	Cascone, et al.[56] 2023	Perioperative	Immunotherapy/ immune CPI	Phase III trial: Induction nivolumab+ chemotherapy followed by adjuvant nivolumab vs induction chemotherapy followed placebo after surgical resection	The peri-operative nivolumab group had improved EFS compared to neoadjuvant chemotherapy group.
AEGEAN	Heymach, et al.[62] 2023	Perioperative	Immunotherapy/ immune CPI	Phase III trial: Induction durvalumab+ chemotherapy followed by adjuvant durvalumab vs induction chemotherapy followed placebo after surgical resection	The peri-operative durvalumab group had improved EFS and pCR compared to neoadjuvant chemotherapy group.
NeoADURA	Tsuboi, et al.[71] 2021	Neoadjuvant	Targeted therapy/ EGFR TKI	Phase III trial: EGFR+ NSCLC received induction osimertinib+/- chemotherapy vs chemotherapy alone followed by surgical resection	On-going Study
NEOS	Lv, et al.[68] 2023	Neoadjuvant	Targeted therapy/ EGFR TKI	Phase II trial: EGFR+ NSCLC received induction osimertinib followed by surgical resection	Neoadjuvant osimertinib is safe and effective in patients with EGFR + NSCLC.
ALNEO	Leonetti, et al.[72] 2021	Neoadjuvant	Targeted therapy/ ALK TKI	Phase II trial: Feasibility neoadjuvant alectinib for ALK+ NSCLC	On-going Study

INT0139	Albain, et al.[42] 2009	Neoadjuvant	Chemoradiation	Phase III trial: Chemoradiation with or without surgical resection for stage IIIA NSCLC	No difference in OS between two groups; in sub-group analysis, the patients who underwent lobectomy had improved OS compared to match cohort with chemorad.
INT0160	Rusch, et al.[49] 2007	Neoadjuvant	Chemoradiation	Phase II trial: Induction concurrent chemoradiation treatment followed by surgical resection for superior sulcus tumor	The induction chemoradiation therapy is feasible and is associated with high complete resection and pCR.
LungART	Pechoux, et al.[79] 2022	Adjuvant	Radiation	Phase III trial: 3D conformal PORT vs no PORT in stage IIIA-N2 NSCLC	PORT was not associated with an improved DFS compared to no PORT.
PORT-C	Hui, et al.[77] 2021	Adjuvant	Radiation	Phase III trial: PORT vs no PORT in resected stage III A-N2 NSCLC + adjuvant chemotherapy	The PORT did not improve OS or DFS.

Table 2. Consensus Summary of Surgical Resectability for Non-Small Cell Lung Cancer

			Non-Bulky		Bulky	
	N0	**N1**	**N2 Single**	**N2 Multi**	**N2 Single**	**N2 Multi**
T1/T2	**Resectable**	**Resectable**	**Resectable**	**Potentially Resectable**	**Potentially Resectable**	**Un-Resectable**
T3	**Resectable**	**Resectable**	**Resectable**	**Potentially Resectable**	**Potentially Resectable**	**Un-Resectable**
T3 (Pancoast)	**Potentially Resectable^{+}**	**Potentially Resectable^{+}**	**Un-Resectable**	**Un-Resectable**	**Un-Resectable**	**Un-Resectable**
T4 Size	**Potentially Resectable**	**Potentially Resectable**	**Un-Resectable**	**Un-Resectable**	**Un-Resectable**	**Un-Resectable**
T4 Satellite	**Potentially Resectable**	**Potentially Resectable**	**Potentially Resectable**	**Un-Resectable**	**Un-Resectable**	**Un-Resectable**
T4 Invasion	**Potentially Resectable**	**Potentially Resectable**	**Un-Resectable**	**Un-Resectable**	**Un-Resectable**	**Un-Resectable**

*The above table represents a general recommendation for the surgical management of locally advanced lung cancer. Every case is unique, and in selected “un-resectable” patients, surgical resection may be considered after a multi-disciplinary discussion in the institutions with expertise.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Samuel S. Kim reports a relationship with Intuitive Surgical Inc that includes: funding grants and speaking and lecture fees. David T Cooke reports a relationship with Bristol Myers Squibb Co that includes: speaking and lecture fees. Biniam Kidane reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory and speaking and lecture fees. Biame Kidane reports a relationship with Merck & Co Inc that includes: consulting or advisory and speaking and lecture fees. Biniam Kidane reports a relationship with Roche that includes: consulting or advisory and speaking and lecture fees. Biniam Kidane reports a relationship with Medtronic that includes: consulting or advisory and speaking and lecture fees. Biniam Kidane reports a relationship with Olympus Corporation that includes: consulting or advisory and speaking and lecture fees. Samuel S. Kim reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Luis Tapia Vargas reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Jyoti Patel reports a relationship with AbbVie Inc that includes: consulting or advisory. Jyoti Patel reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Jyoti Patel reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory. Jyoti Patel reports a relationship with Gilead Sciences Inc that includes: consulting or advisory. Jyoti Patel reports a relationship with Guardant Health Inc that includes: consulting or advisory. Jyoti Patel reports a relationship with Sanofi that includes: consulting or advisory. Jyoti Patel reports a relationship with Tempus that includes: consulting or advisory. Jyoti Patel reports a relationship with AnHeart Therapeutics that includes: consulting or advisory. Jyoti Patel reports a relationship with Blueprint Genetics that includes: consulting or advisory. Jyoti Patel reports a relationship with Black Diamond Therapeutics that includes: consulting or advisory. Joel Neal reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Joel Neal reports a relationship with Genetec Inc that includes: consulting or advisory. Joel Neal reports a relationship with Exelixis Inc that includes: consulting or advisory. Joel Neal reports a relationship with Takeda Pharmaceutical Company Limited that includes: consulting or advisory. Joel Neal reports a relationship with Eli Lilly and Company that includes: consulting or advisory. Joel Neal reports a relationship with Amgen Inc that includes: consulting or advisory. Joel Neal reports a relationship with Sanofi that includes: consulting or advisory. Joel Neal reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory. Joseph Shrager reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Joseph Shrager reports a relationship with Becton Dickinson and Company that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.