Invited expert opinion

Defining Resectability: When Do You Try To Take It Out?

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Abbreviations:
CT computed tomography
CPB cardiopulmonary bypass
EBUS endobronchial ultrasound
EUS esophageal ultrasound
ECMO Extracorporeal Membrane Oxygenation
NCCN National Comprehensive Cancer Network
pCR Pathologic complete response
mPR Major Pathologic response
EFS Event-free survival
HR Hazard Ratio
OS Overall survival
IASLC International Association for the Study of Lung Cancer
ICI Immune Checkpoint Inhibitors
PET-CT Positron emission computed tomography
EORTC European Organisation for Research and Treatment of Cancer
ETOP European Thoracic Oncology Platform
ESTRO European Society of Thoracic Radiation Oncology
ESTS European Society of Thoracic Surgery
ERS European Respiratory Society
ESP European Society of Pathology
MRI Magnetic Resonance Imaging
SAKK Swiss Group for Clinical Cancer Research
HR Hazard ratio

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Central picture:

<table>
<thead>
<tr>
<th>A. Before induction protocol with durvalumab</th>
<th>B. After induction protocol with durvalumab</th>
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</table>

Complete metabolic response to chemoimmunotherapy may not always change resectability though pathological downstaging and complete resection are prognostically significant and encourage us to consider a therapeutic strategy that includes resection for this stage III patient.

Central Message:

A standardized definition of resectability for lung cancer is desirable for treatment allocation with the advent of new induction therapy regimens. Complete resection remains the central objective.

Keywords: immune checkpoint inhibitors, non-small cell lung cancer, surgery, resectability induction therapy, locally advanced non-small cell lung cancer
Introduction

The 5-year survival rates decrease from 92% in patients with resected stage IA1 disease to 36% in patients with stage IIIA disease [1]. Improvements in outcome for locally advanced non-small cell lung cancer (NSCLC) have been achieved via improvements in systemic therapy and proper allocation to local therapy such as surgical resection or radiotherapy. New attractive modalities such as immune checkpoint inhibitors (ICI) in stage IB-IIIIB resectable patients provides promising 2-year overall survival (OS) rates of 83% or 85% [2, 3, 4, 5]. In contrast overall 2-year survival has been reported to be 66.3% if stage III tumors were judged unresectable and treat with concurrent chemoradiotherapy and consolidation ICI. However, poorer performance status scores and the inclusion of stage IIIC patients in the cohort make a head-to-head comparison inappropriate [6]. Given the wish to offer patients the opportunity for the highest probability of disease control, a critical decision point after completion of the diagnostic and staging evaluations is centers on the concept of resectability, which is best determined in a multidisciplinary tumor board setting. Unfortunately, there is no standardized definition of resectability, neither for clinical decision making, nor for inclusion into clinical trials; and definitions vary between available guidelines (Table 1). Additionally, the complexity of defining resectability at baseline presentation is further challenged by the fact that clinical and pathological downstaging occurs in a significant number of patients undergoing induction regimens with ICI alone or in combination with chemotherapy. This downstaging effect results in prolongation of disease-free and overall survival. The objective of this article is to discuss how to define resectability in the midst of these important and evolving paradigms shifts. Medical operability impacting surgical risk, an important though perhaps less plastic or modifiable factor in decision making, will not be discussed.

Definition of Resectability

The aim of any curative intent surgery for primary lung cancer is to achieve a complete resection, otherwise known as an R0 resection [7]. According to the International Association for the Study of Lung Cancer (IASLC) complete resection is defined as:
- En-bloc resection of the tumor with microscopically free margins;
- Systematic lymph node dissection or lobe-specific systematic nodal dissection;
- No extracapsular nodal extension of the tumor;
- The highest mediastinal lymph node negative for tumor;
- Pleural and pericardial cytology negative [7].

If any of these conditions are not fulfilled, the resection is not considered complete by these rigorous standards. Uncertain resections have all margins free of tumors but have not fulfilled all the complete resection criteria [8].

Complete resection and proper documentation of the “R” status in usual practice is recommended. A large data analysis from the IASLC Lung Cancer Staging Project demonstrated that R1 and R2 resections are associated with a significantly poorer survival than R0 (R1 hazard ratio [HR]=1.85, R2 HR=2.14[p<0.0001]): but this remains a prognosis based on historical IASLC data [9]. Similarly, higher rates of recurrence and mortality have been shown for uncertain resections in retrospective studies [10,11].

Nonetheless, this highlights the importance of rigorously determining the precise stage of the tumor locally (T factor) and in the lymph nodes (N factor) by imaging, but also mediastinal staging to assess the probability to achieve a complete resection via upfront surgery. Whereas the T stage is important to assess the technicality of resecting a tumor completely, so is the assessment of N2 disease more a prognostic then a technical factor, as it has been demonstrated that increased nodal involvement impacts survival [12]. However, in patients with bulky or invasive mediastinal lymph node metastases, significant technical considerations can arise much like in invasive T4 stages.

**T staging**

T3 and T4 tumors are not only characterized by their size, the number of lesions present but also by their invasion of local structures ranging from chest wall for T3 tumors to the mediastinum (diaphragm, heart, great vessels, carina, trachea, esophagus, spine) for T4 tumors [1]. Surgery in case of invasion of local structures requires an extended resection to
the organs invaded in order to achieve R0 resection [13]. Initial work-up for assessing resectability of these tumors include:

- Contrast-enhanced chest computed tomography to better define anatomical relations with the surrounding structures;
- Positron emission computed tomography (PET-CT) with 2-deoxy-2-[fluorine-18]fluoro-D-glucose, with/without contrast to search for distant metastases and evaluate mediastinal lymph nodes;
- Invasive mediastinal/nodal staging (endobronchial ultrasound [14], esophageal ultrasound [14, combined EBUS-EUS and mediastinoscopy)
- Chest magnetic resonance imaging to assess extension to the chest wall, the spine, the great vessels, the mediastinum, and in particular in case of “Pancoast”-tumors;
- EUS and cardiac gated magnetic resonance imaging (MRI) or computed tomography (CT) to assess extension to the esophagus or the left atrium;
- Flexible bronchoscopy to evaluate the endoluminal extension to the bronchus tree, the carina or the trachea.

T4 tumors require special attention due to the frequent need for special and multidisciplinary surgical expertise including cardiac or vascular expertise (vena cava, aorta), orthopedic or neurosurgeons (vertebral body) and plastic surgeons (brachial plexus or flap reconstruction). Furthermore, special infrastructural care platforms are required such as access to extracorporeal membrane oxygenation [ECMO] or cardiopulmonary bypass (CPB). Indeed, experienced “know how” from other disciplines such as anaesthesiology and intensive care teams available in specialized centers is essential to an optimal surgical outcome. Some tumor locations such as heart, aorta, trachea and esophagus are generally considered unresectable. However, some rare cases can be R0 resected with the support of ECMO/CPB, complex soft tissue or digestive reconstructive techniques or the preoperative application of endovascular aortic stents (Figure 1). Such advanced surgical expertise is not available in every institution and needs extended training of the lead surgeon and their team of specialized surgical collaborators [15]. Numerous case series have demonstrated that these extended resections
can be performed safely, with good outcome and high R0 rates [13, 15]. The current National Comprehensive Cancer Network (NCCN) guidelines thus recommend considering seeking an additional surgical opinion from a high-volume specialized center if a complete resection is considered uncertain [16].

With a protocol of ipilimumab plus nivolumab and chemoradiotherapy followed by surgery, the INCREASE trial assessed pCR rates, event-free survival and overall survival in a single-arm, prospective phase II trial with either resectable or borderline resectable T3-4N0-1 tumors [17]. In this study, patients considered upfront unresectable were included if expected to be resectable after a chemoradiotherapy and ICI induction protocol. Preliminary results from 25 patients were reported, amongst which were seven Pancoast tumors and four chest wall tumors [18]. With a pCR rate of 60%, it appeared more than twice those reported in recent studies with induction chemotherapy + ICI protocols [2, 3, 4, 18, 19] (Table 2). Despite these outstanding results, over 80% of patients suffered from grade 3 and 4 adverse events, suggesting that such a regimen is only suitable to the fittest of patients. Furthermore, the addition of radiotherapy assures a higher pCR rate in the locoregional basin, but this may not translate to equivalent distant control where most of these patients usually progress. Indeed, high pCR or minimal residual tumor rates of 72% have been previously reported in the Southwest Oncology Group-Intergroup Trial S0220 in patients with superior sulcus tumors (N0-1 M0) treated in a trimodality concept using neoadjuvant chemo-radiotherapy (cisplatin-etoposide and thoracic radiotherapy of 45Gy) followed by surgical resection and adjuvant docetaxel [20]. Despite the excellent pathological response after induction radiotherapy, the 3-year OS was 61% (CI: 44% –74%) and high rates of distant recurrences, particularly in the brain were a major problem [20]. It is possible that intensified systemic therapy will resolve these problems, but additional data are required to address this question.

**Mediastinal staging**

Indication for invasive mediastinal staging are:

- Tumours larger than 3cm;
- Positive lymph nodes on the PET-CT;
- Lymph nodes with small axis superior to 1cm;
- Or central tumors [14].

Mediastinal staging is performed by EBUS and / or EUS in first intention, to determine N2 disease or by EBUS or ultrasound-guided biopsy to eliminate N3 disease [14]. N3 patients are usually not considered candidates for surgery whereas N2 patients are potential surgical candidates after induction treatment [16]. Nodal status is linked to survival and defines which extent of surgery is reasonable. Indeed, analysis from large historical databases showed that patients with N2 disease have significantly worse outcomes compared to patients with N1 and N0 disease [1, 21]: 5-year survival of patients with pN0, pN1, pN2 and pN3 are respectively 75%, 49%, 36% and 20% [12]. However, many of these recommendations are based on historical, real-world data with conventional chemotherapy as induction treatment. In this context it needs to be mentioned that several retrospective analyses and case series have reported encouraging long-term results including 5-year OS of 39% after surgery within a multimodality treatment concept for stage III(N3) NSCLC [22, 23, 24, 25]. Overall, mediastinal staging is important for determining and guiding treatment decision. Intrinsic to these shared decisions between the patient and multi-disciplinary team is a personalized adjustment of risk versus potential benefit of all available treatment modalities. Careful and transparent weighing of short-term risks of the available therapeutic strategies against the potential survival from their stage and biology of disease is critical to a treatment course that will fit with the patient’s overall therapeutic goals. Nevertheless, it is important to remember that these prognostic data do not uniformly represent patients being treated with modern treatment concepts. An update of the N-staging was presented at the 2023 World Conference on Lung Cancer and further stratifies the anatomic classification of NSCLC in the 9th edition of the TNM classification. Yet, it provides no insight to the relevant aspects of lung cancer biology that are becoming part of usual diagnostics in the resectable stages of lung cancer. In the upcoming version, the N-staging will be further subclassified into single- (N2a) and multi-station (N2b) N2 disease: based on the T descriptor, single station N2 tumors are newly classified as UICC-stage II, whereas N2b tumors remain in UICC-stage III. This new classification is set to be applied in
January 2024 [28]. This might equally change our inclusion criteria and assessment of resectability, because historically multi-station N2 disease has been judged as an unresectable stage for many colleagues around the world.

A major problem that surgeons must address is that invasive mediastinal staging is not broadly applied. Many patients are managed based upon clinical staging purely following imaging and this is not a reliable strategy. The risk of both under- and overstaging has been well described in a meta-analysis by Navani et al. and should be minimized in clinical practice [8]. An understaging of nodal disease occurs in up to 34% of cases and is associated with poorer survival due to a potential delay in or lack of receipt of indicated systemic treatment [27]. In contrast, clinical overstaging was seen in 14% of the patients included in the meta-analysis and may result in an exclusion of patients from potentially curative surgery.

When it comes to the decision-making about resectability based on the extent of mediastinal disease, looking at available guidelines, there is no consensus about the degree of mediastinal lymph node invasion which should be considered resectable (Table 1) [28]. The current UK, European and American guidelines use varying definitions for resectable N2 NSCLC ranging from “non-fixed, non-bulky nodes, single zone N2-disease with a reasonable chance of complete resection and clear pathological margins”, to “pathologically proven, low-volume (<3cm), non-invasive lymph nodes” [28]. These criteria are not applicable given the new IASLC mediastinal sub-classification of single and multiple N2, and is based on historical data [28].

The European Organization for Research and Treatment of Cancer (EORTC) - Lung Cancer Group launched a multistep initiative together with other scientific societies involved in lung cancer treatment (European Thoracic Oncology Platform [ETOP], European Society of Thoracic Radiation Oncology [ESTRO], European Society of Thoracic Surgery [ESTS], European Respiratory Society [ERS], IASLC, European Society of Pathology [ESP]) to find a definition for resectability to be used in future clinical trials. In the conclusion, areas of future research interest were largely defined by the challenge of multiple-station N2 tumors.

*Defining resectability in the era of immunotherapy trials*
Results from several phase II and III trials with immune checkpoint inhibitors in stage IIA to IIIB patients showed unprecedented rates of pathological complete responses. High rates of tumoral and nodal downstaging, including the context of multistation N2 disease, and the major reduction in subsequent distant metastasis have changed the concept of resectability by rendering a single static definition very challenging to outline (Table 1) [2-3].

In a single-arm multicenter phase II trial, the Swiss Group for Clinical Cancer Research (SAKK) evaluated the additional benefit of durvalumab with induction chemotherapy (cisplatin and docetaxel) in patients with stage IIIA (N2) non-small cell lung cancer [29]. Compared to a historical cohort of stage III (N2) patients treated by induction chemotherapy (cisplatin and docetaxel) followed by surgery where one-year EFS rate was 48%, the addition of peri-operative durvalumab helped achieve a one-year event-free survival (EFS) of 73%. Major pathologic response (MPR) was 62% and pCR was 18%. Nodal downstaging was confirmed in 67% of patients: nodal downstaging to ypN1 occurred in 11 (20%) of 55 patients, whereas ypN0 was found in 26 (47%) of 55 patients. There was no information on multistation N2 or bulky N2 tumors.

Similar results were found in the NADIM trial with an overall survival of 85% at two years in stage IIIA and IIIB patients who had received induction chemotherapy plus nivolumab followed by adjuvant nivolumab. The NADIM II trial has highlighted the potential long-term benefits of ICI in this highly heterogenous patient group [3]. The overall survival benefit for the addition of peri-operative nivolumab was highly significant ([HR for death, 0.43; 95% CI, 0.19 to 0.98]). R0 resection was achieved in 94% and 85% of the patients in the treatment arm and the control arm, respectively. This study was marked by a high rate of N2 disease in the nivolumab plus chemotherapy group (n=41 [72%]) compared to the chemotherapy alone group (n=16 [55%]): more than half of the patients had multistation N2 disease but there was no mention of bulky N2 [3]. The downstaging rate was 69.8% in the nivolumab arm vs 40% in the chemotherapy arm (OR, 3.47; 95% CI, 1.19-10.1; P = .04). Six pneumonectomies (10.3%)
were performed in the treatment arm and two pneumonectomies (10%) in the control arm. In the treatment arm, 15 patients with T3 Tumors (26.3%) and 14 patients with T4 tumors (24.6%) were included compared to 6 (20%) T3 tumours and 12 (41%) T4 tumors included in the control arm. These imbalances in the T-stage could explain the above-mentioned difference in the R0 resection rate and highlight the importance of phase 3 blinded and stage-stratified trials.

Benefits of ICI in combination with conventional chemotherapy for patients with resectable tumors has lately also been confirmed in phase 3 trials. Checkmate 816, a randomized controlled open-label trial, has helped established nivolumab as a standard protocol treatment for induction therapy in patients with stage II to IIIA disease [2]. Indeed, by evaluating efficacy and safety of induction nivolumab plus chemotherapy (three cycles) compared to chemotherapy alone (three cycles) in patients with resectable NSCLC, median EFS was significantly improved with nivolumab (31.6 months versus 20.8 months; p=0.005). The HR for disease progression, disease recurrence, or death was 0.63 (97.38% CI, 0.43–0.91, P=0.005) and the percentage of patients with pCR was 24% with nivolumab compared to 2.2% without (p<0.001) [2]. R0 resection was achieved in 83.2% and 77.8% of the patients in the treatment arm and the placebo arm, respectively. Resectability and the operative approach was determined by the surgeon; lobectomy, bi-lobectomy and pneumonectomy, as well as sleeve-resections were allowed. Twenty-five pneumonectomies (16.8%) were performed in the treatment group and 34 pneumonectomies (25.2%) in the control arm. There was no information on T3-T4 tumors. Patients deemed resectable by the investigator team with cT1-4 N0-2 were eligible for inclusion in this study. However, details of T4 extent, multiplicity of N2 or bulkiness at baseline were not captured in the original data collection forms.

Recently, the interim results of the Checkmate 77t assessing perioperative nivolumab plus chemotherapy in resectable stage IIA-IIIB NSCLC were presented [30]. In this phase 3, randomized, double-blind trial, patients were randomized to receive neoadjuvant nivolumab plus chemotherapy followed by adjuvant nivolumab (NIVO + chemo/NIVO group) or
neoadjuvant chemotherapy plus placebo followed by adjuvant placebo (chemo/placebo group) \(^{30}\). At a minimum follow-up of 15.7 months, the interim results show a significantly improved median EFS in the NIVO + chemo/NIVO group when compared to the chemo/placebo group (median [95% CI], not reached [28.9 months–not reached] vs 18.4 months [13.6–28.1]; HR [97.36% CI], 0.58 [0.42–0.81]; \(P = 0.00025\) \(^{30}\). Similarly to the Checkmate 816 trial, pCR rates were significantly higher in the NIVO + chemo/NIVO group compared to the chemo/placebo group (25.3% versus 4.7%; OR 6.64; 95% CI 3.40–12.97) \(^{30}\).

The Keynote-671 trial is a randomized, double-blind phase 3 trial where patients with resectable stage II, IIIA or IIIB (N2) NSCLC were assigned to receive either induction pembrolizumab plus cisplatin-based chemotherapy or induction placebo plus cisplatin, followed by surgical resection and adjuvant pembrolizumab or placebo \(^{[5]}\). A recently published first interim analysis showed a significantly improved EFS and an increased pCR (18.1% in the treatment arm versus 4.0% in the placebo arm). In addition, a numerically higher percentage of nodal downstaging was seen in the treatment arm (downstaging to N0: 34.3% vs. 23.4%). A post-hoc analysis of EFS showed that the EFS benefit of the treatment arm is only seen in the subgroup who received surgical resection (HR [95% CI] 0.53 [0.42 – 0.67]) and in the subgroup where R0 resection is achieved (HR [95% CI] 0.53 [0.41 – 0.68]) (results presented at the 60th Annual Meeting of The Society of Thoracic Surgeons, 2024). Resectability was determined by surgical consultation and an investigator assessment. Lobectomy was the most common surgical procedure in both groups (treatment arm 78.8%, placebo arm 75.1%), followed by pneumonectomy (treatment arm 11.4%, placebo arm 12.3%). Ninety-two percent of patients in the treatment arm had an R0 resection while 84.2% of patients in the control arm had an R0 resection. A hundred and twenty-one T3 Tumors (30.5%) and 115 T4 Tumors (29%) were included in the treatment group compared to 109 T3 tumors (27.2%) and 104 T4 tumors (26.0%) included in the control group. A hundred and sixty-eight patients (42.3%) had N2 disease in the treatment arm compared to 187 patients (46.8%)
in the control group. There was no information about inclusion of N2 multistation and/or bulky N2 disease among these patients.

In the AEGEAN trial – a randomized, double-blind, phase 3-trial - 802 treatment-naive patients with resectable stage II-IIIB (N2) NSCLC were assigned to either induction durvalumab plus platinum-based chemotherapy or induction placebo plus platinum, followed by surgical resection and adjuvant durvalumab or placebo [6]. Surgery was performed in 77.6% and 76.7% of patients in the treatment arm and the placebo arm, respectively. The recent presentation of the results showed that pCR was achieved in 17.2% in the treatment arm vs 4.3% in the placebo arm. Median EFS was not reached in the treatment arm and thereby significantly prolonged when compared to the EFS of 25.9 months in the placebo arm. 94.7% of patients in the treatment arm had an R0 resection while 91.3% of patients in the control arm had an R0 resection. In the AEGEAN trial, resectability was based on both the IASLC Staging Manual in Thoracic Oncology (version 8) and the opinion of a multidisciplinary evaluation. However, the planned surgical procedure needed to comprise of either a lobectomy, a sleeve lobectomy or a bilobectomy. No information has been yet published on T3 and T4 tumors but all candidates with locally advanced tumors requiring pneumonectomy where therefore excluded. Similar results from the Neotorch trial - a randomized, double-blind, placebo-controlled, phase III trial, evaluating Toripalimab plus chemotherapy followed by Toripalimab maintenance vs chemotherapy in stage III resectable non-squamous NSCLC, without EGFR/ALK alterations- are reported [19]. 202 patients were recruited in each group. EFS was significantly improved in the Toripalimab arm (hazard ratio [HR] = 0.40, 95% CI [0.277-0.565], p<0.0001). The MPR and the pCR rates were also higher in the Toripalimab arm, 48.5% vs 8.4% and 24.8% vs 1.0% respectively. Overall survival results are not yet available. 95.8% of patients in the treatment arm had an R0 resection while 92.6% of patients in the control arm had an R0 resection. No information was yet available on N2 tumors as well as T3-T4 tumors.
Table 2 and 3 highlight the results from the phase II-III randomized trials on adjuvant ICIs for resectable NSCLC that are already published or currently ongoing: they show a range of pCR from 17.2% to 37% and EFS of 62.4% to 73.2% at 2 years.

In comparison to this stands the PACIFIC trial, where 709 patients with unresectable stage III NSCLC were randomized to receive consolidation therapy (236 patients received placebo and 473 received durvalumab) after definitive chemoradiotherapy [6]. The median progression-free survival in patients treated with durvalumab compared to the placebo was significantly improved (16.8 months vs 5.6 months; HR 0.52 [95%CI, 0.42 to 0.65; p<0.001). The 2-year OS was significantly higher in the durvalumab group compared to the placebo group (66.3 % vs 55.6%; p<0.0025), as well as the 5-year OS (42.9% versus 33.4%) 6, 31. In the PACIFIC trial, resectability was defined according to the 7th edition of the IASLC Staging Manual in Thoracic Oncology [31]. However, no standardized protocol for the definition of resectability was used before trial inclusion, nor was a surgical opinion required. The application of the PACIFIC trial protocol is a valuable option for primarily unresectable stage III patients and especially for patients who are deemed inoperable due to limited cardiorespiratory reserve and/or other comorbidities.

Conclusion
Anatomical lung resection remains a key and ever-growing element in management of locally advanced NSCLC within multimodality treatment. In order to achieve an R0 resection which guarantees the best OS rate, systemic treatment options have been reinforced by ICI. Concurrent chemotherapy with ICI promotes downstaging and increases pathological response, which translate to better event-free and overall survival. Accordingly, in multidisciplinary tumor boards, induction treatment protocols have evolved towards chemoimmunotherapy for stage II-IIIA patients, especially with confirmed N2 disease or tumors larger than 4cm. This approach is also considered in more borderline situations where patients with complex T4 disease and/or extensive nodal involvement such as multiple or bulky N2
should be assessed on a case-by-case basis. In the light of the promising results of the available phase 2 and 3 trials investigating induction chemoinmunotherapy, we expect a continued paradigm shift in the resectability assessment of locally advanced NSCLC in the future. Initial results from trials assessing the value of triple induction by adding radiotherapy to turn unresectable tumors into resectable ones have shown even more promising response rates. Given the outstanding response rates, re-evaluation of resectability should eventually considered after completion of induction and re-staging for borderline patients. At this time information on radiological and metabolic response can be integrated into the decision-making process. Of course, the counterpoint will emerge if we can accurately predict the occurrence of PCR prior to resection – will resection still be required? Without a doubt, future trials will need to track much more granular clinical staging information throughout the trajectory of treatment and consider resectability at baseline, after completion of induction and benchmarked to the operation performed and whether it yielded an R0 resection. This approach should provide better guidance for patient in special subsets who were traditionally are deemed unresectable such as T4 or multistation/bulky N2 tumors.

Until then, surgical indication depends on a multidisciplinary discussion involving surgeons, radiation oncologists, pathologists, medical oncologist and radiologists who will integrate all available data upon the backdrop of each patient’s goals of care and risk tolerance. If a surgeon or center is uncertain about potential complete resection, they should consider obtaining an additional multi-disciplinary team evaluation from a high-volume center with the required specialized surgical expertise.
**Figures and Tables**

**Figure 1:** Figure 1: a 66-year-old patient was admitted to our department for a cT2 cN0 cM0 left central squamous cell carcinoma invading the descending thoracic aorta (A). After partial response from induction treatment using the Checkmate 816 protocol, an aortic stentgraft was placed before surgery (B). Separation of the tumor from the aorta (C). End-result after extended left pneumonectomy and dissection along the aortic adventitia (D).
### Table 1: Summary of UK, European and American guidelines on the management of potentially resectable N2 NSCLC

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Definition of «resectable»</th>
<th>Recommendations</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>BTS and SCTS (2010)</td>
<td>Non-fixed lymph nodes Non-bulky lymph nodes Single-zone N2 disease Reasonable chance of: Complete resection Clear pathological margins</td>
<td>Consider surgery as part of multimodality treatment in non-fixed, nonbulky, single-zone N2 NSCLC Further research into the role of surgery in non-fixed, non-bulky, multi-zone N2 NSCLC</td>
<td>Significant weight placed on IASLC staging database outcomes despite lack of comparator group and lack of clinical N2 Guidelines consider evidence for adjuvant chemotherapy more robust than pre-operative chemotherapy</td>
</tr>
<tr>
<td>ACCP (2013)</td>
<td>Discrete lymph nodes Easily measurable and defined lymph nodes Free from major structures, such as the great vessels and trachea</td>
<td>Definitive CRT or induction therapy (chemotherapy or CRT) followed by surgery Surgery followed by adjuvant chemotherapy not recommended</td>
<td>Does not support the concept that surgery can only be justified in patients with minimal N2 disease Pre-operative chemotherapy better than surgery alone in all NSCLC (small studies) and therefore surgery plus adjuvant chemotherapy is not recommended</td>
</tr>
<tr>
<td>ESMO (2017)</td>
<td>Minimal, non-bulky N2 disease Single-station N2 disease</td>
<td>Definitive CRT, induction chemotherapy followed by surgery or induction CRT followed by surgery</td>
<td>Paramount importance of an experienced and high-volume multi-disciplinary team (MDT) and treatment centres able to minimise risk and complications from multi-modality treatment highlighted</td>
</tr>
<tr>
<td>NICE (2019)</td>
<td>None provided</td>
<td>Consider CRT followed by surgery</td>
<td>CRT followed by surgery improves PFS and might improve survival compared with CRT alone</td>
</tr>
<tr>
<td>NCCN (2023)</td>
<td>Single lymph node smaller than 3 cm</td>
<td>Definitive CRT or induction chemotherapy followed by surgery or induction CRT followed by surgery Maintenance durvalumab following cCRT</td>
<td>Benefit from pre-operative chemotherapy is similar to that of post-operative chemotherapy and either approach is justified</td>
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This table, under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), was duplicated and updated from a previous table done by Dr Matthew Evison [28]. ACCP American College of Chest Physicians, BTS British Thoracic Society, CRT chemoradiotherapy, cCRT concurrent chemoradiotherapy, ESMO European Society of Medical Oncology, IASLC International Association for the Study of Lung Cancer, NICE National Institute for Health and Care Excellence, NCCN National Comprehensive Cancer Network, NSCLC non-small cell lung cancer, PFS progression-free survival, SCTS The Society for Cardiothoracic Surgery in Great Britain and Ireland.
**Table 2:** Main results from phase III randomized trials on induction immune checkpoint inhibitors for resectable NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant</th>
<th>N</th>
<th>Adjuvant</th>
<th>Stage</th>
<th>Primary Endpoint</th>
<th>Preoperativ e patient attrition</th>
<th>DFS or EFS HR</th>
<th>OS HR</th>
<th>DFS or EFS</th>
<th>OS</th>
<th>R0</th>
<th>pCR</th>
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<tr>
<td><strong>Neoadjuvant or perioperative (neoadjuvant + adjuvant)</strong></td>
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<tr>
<td><strong>AEGEAN</strong> [4]</td>
<td>Durvalumab + CT vs CT (4cycles; 12 weeks)</td>
<td>802</td>
<td>Durvalumab vs supportive care</td>
<td>IIA – IIIB</td>
<td>pCR EFS</td>
<td>19% vs 19%</td>
<td>0.68 (p&lt;0.004)</td>
<td>NR</td>
<td>73.2% vs 63% at 2 yrs</td>
<td>NR</td>
<td>94.7 vs 91.3%</td>
<td>17.2 vs 4.3%</td>
</tr>
<tr>
<td><strong>Checkmate -816</strong> [2]</td>
<td>Nivolumab + CT vs CT (3cycles)</td>
<td>358</td>
<td>None</td>
<td>IB to IIA</td>
<td>pCR EFS</td>
<td>16% vs 21%</td>
<td>0.63; 97.38% CI, 0.43 to 0.91; P = 0.005</td>
<td>0.57 (99.67% CI, 0.30 to 1.07)</td>
<td>Median EFS 31.6 months vs 20.8 months</td>
<td>83% at 2 yrs</td>
<td>78% at 3 yrs</td>
<td>83.2 vs 77.8%</td>
</tr>
<tr>
<td><strong>Keynote-671</strong> [5]</td>
<td>Pembrolizumab + CT vs CT (4cycles; 12 weeks)</td>
<td>797</td>
<td>Pembrolizumab vs supportive care</td>
<td>II-IIIB</td>
<td>EFS OS</td>
<td>18% vs 21%</td>
<td>HR 0.58 (95% CI, 0.46-0.72); P&lt;0.00001</td>
<td>HR 0.73 (95% CI, 0.54-0.99); P=0.02124</td>
<td>(2-year EFS rate, 62.4% vs 40.6%)</td>
<td>NR</td>
<td>92 vs 84.2%</td>
<td>18.1 vs 4%</td>
</tr>
</tbody>
</table>
Neotorch

| Neotorch | Toripalimab + CT vs CT (3 cycles) | Toripalimab vs supportive care after one cycle CT | II-III | EFS | MPR | 18% vs 27% | HR=0.40; 95% CI (0.277-0.565), P<0.0001 | NR | Median NR vs NR | 15.1 months | 95.8 vs 92.6% | 24.8 vs 1% |

Table 3: Subgroup analysis from phase III randomized trials on induction immune checkpoint inhibitors for resectable NSCLC.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>HR (95% CI)</th>
<th>Subgroup</th>
<th>N</th>
<th>HR (95% CI)</th>
<th>Subgroup</th>
<th>N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease stage</td>
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<td></td>
<td>Disease stage</td>
<td></td>
<td></td>
<td>Disease stage</td>
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<tr>
<td>II</td>
<td>214</td>
<td>0.76 (0.43-1.34)</td>
<td>II</td>
<td>239</td>
<td>0.65 (0.42-1.01)</td>
<td>IB-II</td>
<td>126</td>
<td>0.94</td>
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<td>IIIA</td>
<td>338</td>
<td>0.67 (0.39-0.83)</td>
<td>IIIA</td>
<td>442</td>
<td>0.64 (0.41-0.72)</td>
<td>IIIA</td>
<td>229</td>
<td>0.57</td>
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<tr>
<td>IIIB</td>
<td>189</td>
<td>0.83 (0.52-1.32)</td>
<td>IIIB</td>
<td>116</td>
<td>0.52 (0.31-0.89)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
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<td>Nodal status</td>
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<td>Nodal status</td>
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<td></td>
</tr>
<tr>
<td>N2 single</td>
<td>273</td>
<td>0.61 (0.30-0.94)</td>
<td>N0</td>
<td>290</td>
<td>0.67 (0.40-0.82)</td>
<td>N2 single</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>N2 multi</td>
<td>74</td>
<td>0.69 (0.33-1.38)</td>
<td>N1</td>
<td>152</td>
<td>0.60 (0.36-1.01)</td>
<td>N2 multi</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N2</td>
<td>355</td>
<td>0.57 (0.42-0.78)</td>
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</tr>
</tbody>
</table>
Acknowledgement: The authors would like to thank Dr Olivia Theisen-Lauk for helping with the case presented in Figure 1.
References


Complete metabolic response to chemoimmunotherapy may not always change resectability though pathological downstaging and complete resection are prognostically significant and encourage us to consider a therapeutic strategy that includes resection for this stage III patient.