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# The Role of Surgery in Management of Locally Advanced Non-Small Cell Lung Cancer

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## Opinion statement

Patients with locally advanced non-small cell lung cancer (NSCLC) are treated for cure, but treatment decisions are not straightforward. Chemotherapy is essential due to the high risk of systemic relapse, but local therapy is also required for cure. In the small subset of stage III patients with N0 or N1 disease, surgery is typically the initial therapy and extended resections are frequent. The majority of IIIA patients present with N2 disease and treatment paradigms for these patients are controversial, particularly concerning the role of resection. Surgery has a limited role in bulky IIIA, IIIB, and IIIC disease, which is typically treated with combined systemic therapy and radiation. The authors believe that in resectable IIIA disease, the addition of surgery to multimodality treatment appears to improve local control and overall survival. Induction therapy is essential, and the use of chemotherapy alone or chemoradiotherapy remains an area of debate. Pneumonectomy should be used with caution in IIIA disease, as numerous prospective trials have noted excessive perioperative mortality. The introduction of immunotherapies in this stage may quickly transform treatment decisions.

## Introduction

In 2018, more than 200,000 people in the USA will be diagnosed with lung cancer [1]. For both men and women, lung cancer is responsible for the majority of cancer-related deaths, worldwide [2]. A minority of patients present with localized, early-stage disease curable with single modality therapy; however, most present in later stages with cure often reliant upon a multimodality approach. Patients with advanced, metastatic non-small cell lung cancer (NSCLC) rarely undergo curative-intent resections. However, for those with locally advanced tumors, treatment paradigms are more nuanced and employ various combinations of systemic therapy, radiation, and surgery.

Patients with stage III tumors can achieve cure in 10–30% of cases [3, 4]. While radiotherapy or surgical resection can lead to local control, systemic therapy is considered necessary to achieve long-term survival. How best to combine modalities has been debated for decades. Immunotherapies have revolutionized the treatment of advanced NSCLC and with emerging evidence for utilization in stage III disease, and have the potential to further nuance treatment decisions and the role of surgery.

# The scope of stage III disease

Stage III encompasses a wide range of clinical scenarios. The eighth edition of the American Joint of Committee on Cancer's tumor (T), node (N), and metastasis (M) system of staging classifies locally advanced disease as IIIA, IIIB, and IIIC [5]. While technical advancements have made complex resections of large, locally invasive tumors feasible, there is limited evidence that supports extended resections for curative intent for patients with large and infiltrative tumors in the setting of mediastinal nodal disease or for patients with N3 nodal involvement. In other words, surgery is not typically recommended for stage IIIB disease (N2 mediastinal lymph nodes and tumors ≥ T3 or N3 nodal involvement with smaller, < T3 tumors) or for patients with stage IIIC disease (≥ T3 in the presence of N3 nodal involvement). Stage IIIA disease encompasses a select group of patients with large tumors and no mediastinal nodal involvement (T3N1, T4N0, or T4N1), as well as those with smaller tumors (T1 or T2) and N2 mediastinal disease. While all falling under the umbrella of stage IIIA disease, this group is heterogeneous and should be approached with variable treatment plans.

Generally, stage IIIA patients without mediastinal nodal involvement are approached in a similar fashion as stage II cancer with resection followed by adjuvant systemic therapy. For patients with IIIA N2 disease, the role of surgery is more variable. Outcomes and advisability of resection are largely determined by patient factors as well as the bulk and extent of nodal involvement, but there are some that question the utility of surgery at all in this population.

# Does surgery have a role in IIIA N2 NSCLC?

The majority of newly diagnosed patients with stage IIIA NSCLC present with mediastinal node (N2) involvement. While long-term prognoses are generally poor, significant outcome heterogeneity exists. By AJCC staging, patients with microscopic single station nodal disease are grouped in the same category as those with extensive, bulky, multi-station nodal disease despite the fact that the

two groups have different treatment options and outcomes. Among patients with IIIA N2 disease, the bulk and extent of nodal involvement are generally more impactful on treatment decisions than are primary tumor characteristics [6]. The inclusion of surgery in treatment for these patients has been debated at length. Historically, cohorts that include surgery tend to have improved survival compared to those that do not, but much of this survival benefit is attributed to improved patient selection. High quality prospective evidence for a survival advantage with the addition of surgery to treatment is lacking. Those in support of surgery argue that resection improves rates of local control, which is essential for cure.

Opinions of providers are a major driver of clinical decision making when evidence is lacking, and in this situation, institutional and specialty bias is common. In a 2012 survey of 513 thoracic surgeons, Veeramachaneni showed that when confronted with a patient with single-station low-volume N2 disease, 96% of surgeons would recommend surgery as part of multi-modality therapy. When confronted with a patient with bulky multi-station N2 disease, 82% continued to recommend surgery as part of therapy [7]. In a similar survey of medical oncologists by Tanner et al., 92% shared the opinion of thoracic surgeons with regard to single-station low volume disease, but in the setting of multi-station N2 disease, less than half of medical oncologists felt that resection was beneficial [8].

The 2009 North American Intergroup Trial (INT) 0139 remains one of the most influential trials to evaluate surgery for stage III NSCLC. Patients received concurrent chemotherapy plus radiation to 45 Gy and were randomized to surgical resection or continued radiotherapy. All patients received consolidation chemotherapy. The trial failed to identify a difference in overall survival (OS) between groups (median 23.6 months in the surgical arm versus 22.2 months in the standard therapy arm), although patients in the surgical arm were noted to have increased progression-free survival (PFS) (12.8 months versus 10.5 months). INT 0139 reinforced several important observations which had been previously noted in smaller retrospective single institution studies: (1) Patients with N0 disease at thoracotomy experienced notably longer median OS (34.4 months versus 26.4 months), and (2) patients undergoing pneumonectomy, as opposed to lobectomy, had worse short and long-term outcome [9]. In a highly debated post hoc analysis, lobectomy patients were noted to have improved survival compared to matched non-operative patients and the reverse was true for the pneumonectomy cohort. The pneumonectomy patients experienced excessive perioperative mortality and never recouped the benefit in long-term outcome, reinforcing the concept that pneumonectomy may have limited use in settings that require induction therapy. These two observations have driven significant controversy related to surgery in stage III for decades.

## Who is most likely to benefit from resection?

Minimizing morbidity and maximizing therapeutic benefit in patients with stage III disease is highly dependent on careful patient selection. Multiple patient and tumor characteristics are associated with improved outcomes—chief among them is extent of nodal disease. Among studies investigating treatment for IIIA N2 disease, the terms “bulky,” “extensive,” and

"infiltrative" are frequently employed and are widely recognized to be associated with poor prognoses [6, 10–12]. The degree of N2 involvement is categorized into three broad groups: (1) incidental or occult, (2) clinically evident and potentially resectable, and (3) bulky unresectable disease. Occult N2 disease is only found at resection in patients who were thought to be N0 or N1 following appropriate preoperative staging. Potentially resectable N2 disease is that which is identified during initial clinical staging and confirmed with biopsy. Nodes are usually individually discernable, < 3 cm, and discrete from the primary tumor. Patients with unresectable N2 disease have bulky nodes that cannot be individually identified or encase vessels or airways.

A classic study by Andre and colleagues followed 700 patients who underwent resection of N2+ stage IIIA disease and stratified survival according to amount of N2 involvement: single versus multi-station, and if clinically apparent on pre-operative CT or not. Overall survival for those with radiographically undetectable single station disease (so-called "N2 occult") was 34%, compared to only 3% for patients with clinically apparent multi-station disease [11]. While staging and treatments have evolved, the survival difference is striking for patients with IIIA disease.

As in other cancers, response to induction therapy is an important prognostic marker. Pataer and colleagues examined tissue specimens from 358 patients with resected IIIA NSCLC following induction chemotherapy and correlated the percentage of residual viable tumor cells with outcomes. Those with ≤ 10% residual viable tumor were defined as having a major pathologic response (MPR) and had significantly prolonged OS and PFS compared to those with higher volumes of residual disease [13]. Tumor response to induction therapy was also one of the significant findings in the INT 0139 trial. Patients with mediastinal disease clearance (ypN0) experienced extended OS (34.4 months) compared to those with residual nodal disease (26.4 months). Similarly, in Radiation Therapy Oncology Group (RTOG) trial 0229, Suntharalingam and colleagues showed that following trimodality therapy, patients with ypN0 tumors had improved overall survival [14]. As such, MPR and mediastinal downstaging following neoadjuvant therapy are thought to be significant positive prognostic signs. It remains unclear if the significance is related to establishing local control, or if the response is a signal for improved tumor response systemically.

## Patients with residual N2 disease after induction therapy

Since residual tumor in mediastinal lymph nodes following induction therapy is a poor prognostic indicator, establishing mediastinal nodal clearance to induction therapy is considered by many to be an important determination prior to exposing patients to the potential morbidity of resection. In general, patients who experience radiographic tumor progression during induction therapy fare poorly and should not be considered surgical candidates [4]. An exception to this is with the use of immune checkpoint inhibitors in the induction setting. Radiographic and pathologic responses do not correlate with these agents, and increase in nodal size is common and is the result of immune cell infiltration as opposed to tumor progression [15]. For most N2 patients, response to induction therapy cannot be reliably judged with imaging alone, as

neither PET nor CT can accurately predict response in a time frame needed to make a decision regarding resection. Repeat nodal sampling can be challenging but offers critical prognostic information, and some feel that it should be performed prior to resection. For those who feel post-induction pathologic sampling of mediastinal lymph nodes is essential, a plan of endobronchial ultrasound (EBUS) with biopsy at the time of initial staging and reservation of mediastinoscopy following induction is the preferred approach.

Not all providers believe that residual N2 disease after neoadjuvant therapy is a contraindication to resection. In subsets of multiple trials, 5-year OS for patients undergoing R0 resections of ypN2 tumors has been shown to range from 9 to 29% [16–18]. While low, this still eclipses outcomes when surgery is not offered, and decisions should be made on a case-by-case basis. Cerfolio and colleagues conducted a retrospective analysis of their experience treating 402 N2 + patients. Two hundred fifty-three patients did not undergo resection and experienced 5-year overall survival of 8%. One hundred forty-nine patients underwent restaging and attempted resection. Of those identified to have a pathologic complete response, 5-year OS was observed to be 53%. Overall survival was 49% for patients with partial responses to neoadjuvant therapy. The authors conclude that in a selected group of patients with non-bulky N2 disease, response to induction therapy portends a favorable prognosis and that surgical resection should be considered for patients with residual N2 disease following neoadjuvant therapy [17].

## Patients requiring pneumonectomy

Wide ranges of outcomes are reported for patients requiring pneumonectomy for stage III disease. Generally, pneumonectomy is recognized to carry an increased risk of perioperative morbidity and mortality even in earlier stage disease and without induction therapy. Those risks appear to increase with the addition of induction chemotherapy, and there is a perceived incremental increased risk with the use of pre-operative radiation. Multiple single institution trials have shown acceptable perioperative risk for pneumonectomy in this setting, even with induction radiation, but larger multi-center prospective trials report mortality of 5–27%, far in excess to what is reported for lobectomy [19, 20••].

In the INT 0139 trial, a significant number of patients (30%) underwent pneumonectomy and perioperative mortality for that group was 27% compared to 1% mortality for patients undergoing lobectomy. However, it is important to note that intergroup 0139 included patients with bulky N2 disease and that general thoracic surgeons did not perform the majority of resections [9]. Smaller single institution studies have shown that pneumonectomy can be performed safely in the post-induction setting at high-volume centers with general thoracic surgical expertise [21].

A recent multi-institutional trial from Europe prospectively investigated the addition of radiation therapy to standard induction chemotherapy in 232 patients with resectable IIIA N2 disease. A comparably large number of patients in each arm underwent pneumonectomy—20% in the trimodality group and

25% in the bimodality group. All resections were performed at high-volume, experienced surgical centers. Perioperative mortality was only 4.5% in those undergoing pneumonectomy, but this was still five times higher than the 0.8% mortality reported for those undergoing lobectomy, with no difference in survival metrics between tri- and bi-modality induction therapy [20••]. Pneumonectomy undoubtedly places patients at higher risk for complications, and the debate over appropriateness of its use in N2 remains controversial. A meta-analysis by Kim et al. examined perioperative mortality rates for pneumonectomy after induction therapy in 27 trials, half of which included radiation. Mortality was 7% at 30 days and 12% at 90 days, with mortality two times higher for right compared to left pneumonectomy, but no difference in mortality was noted with the inclusion of radiation in the induction treatment [19].

## Induction therapy

For patients with stage IIIA NSCLC undergoing surgery, induction therapy is the standard of care. Some argue for the benefit of upfront resection for single station N2 disease, but a benefit to this approach has not been demonstrated in prospective trials. Induction treatment has the potential to downstage tumors, increase operability, define tumor biology prior to resection, and target potential micrometastatic disease. When appropriately applied, induction chemotherapy has been shown to improve overall survival, time to distant recurrence, and recurrence free survival compared to surgery alone [22]. The addition of radiation to neoadjuvant protocols increases rates of mediastinal nodal clearance and local control. However, pre-operative radiation is associated with increased rates of esophagitis and pneumonitis, and many feel that it increases surgical difficulty of resection, although increased morbidity and mortality have not been reported [9, 20••, 23, 24] (Table 1). The more important question is whether increased nodal clearance and local control seen with inclusion of radiation preoperatively translate to improved OS. Numerous retrospective analyses, randomized controlled trials, and subsequent meta-analyses have evaluated the benefit of adding radiation to neoadjuvant chemotherapy [20••, 25–32].

The recent trial from Pless and colleagues randomized patients at multiple European centers with pathologically proven IIIA/N2 disease to sequential neoadjuvant chemotherapy and radiation or chemotherapy alone. They found no significant difference in median OS with the addition of radiation therapy to pre-operative chemotherapy (37.1 months versus 26.2 months) [20••]. Some question if the sequential approach in this trial may have limited some of the potential benefit from radiation. A recent meta-analysis also addressed the question of bi-modality versus tri-modality approach for IIIA disease. It noted more frequent tumor downstaging, increased mediastinal nodal clearance, increased rates of pathologic complete responses, and improved local control with the use of radiation, but failed to note an improvement in OS [27].

## Surgical principles for resection in stage III disease

The surgeon must approach the patient with locally advanced disease with care. Frequently, patients are nutritionally and functionally debilitated by disease

**Table 1. Prospective multi-institutional trials of neoadjuvant therapy and resection for stage III NSCLC**

| Trial | Year | Treatment | # | Stage | Operative mortality | | Pathologic complete response | | Overall survival | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CRS | CS | CRS | CS | CRS | CS | CR |
| INT0139 [9] | 2009 | CRS vs. CR | 429 | IIIA/IIIB | 8% | N/A | 14% | N/A | 24 months | N/A | 22 months |
| ESPATUE [23] | 2015 | CRS vs. CR | 161 | IIIA/IIIB | 6% | N/A | 33% | N/A | 40% (5 year) | N/A | 44% (5 year) |
| SAAK [20] | 2015 | CRS vs. CS | 232 | IIIA (N2) | 0% | 3% | 16% | 12% | 37 months | 26 months | N/A |
| RTOG 0229/0839 (24) | 2017 | CRS | 93 | IIIA (N2) | 4% | N/A | 25% | N/A | N/A | N/A | N/A |

# number, *C* chemotherapy, *R* radiotherapy, *S* surgery, *SAKK* Swiss Group for Clinical Cancer Research

and induction therapy. Pre-operative evaluation should place extra attention on functional status and judicious use of pre-surgical optimization. If necessary, patients should receive nutritional support and physical therapy during induction therapy to prepare them for resection.

Following induction therapy, repeat staging with PET and CT, complete physiologic re-evaluation, and repeat multidisciplinary discussion at a tumor board according to institutional practices are recommended, and some experts encourage repeat invasive mediastinal staging. Surgical resection should be timely, and not delayed beyond 6–12 weeks after completion of induction therapy to lessen impact of scarring and fibrosis. The operative surgeon should be included in up-front decision-making and treatment planning and should be in close coordination with medical and radiation oncology in order to avoid delays.

At resection, the surgeon should plan for full lymph node evaluation in order to guide adjuvant therapies and provide prognostic information. Hilar dissection and should be performed with care, as significant inflammation and treatment response can be encountered. Buttressing of the bronchial closures with healthy, live tissue such as pleura, muscle, thymus, pericardial fat, or even omentum is recommended. Patients requiring pneumonectomy should be considered for referral to general thoracic surgeons at high volume centers with expertise in these resections.

Importantly, disease stage and the use of induction therapy do not negate a potential minimally invasive resection. Yang and colleagues examined their single institution outcomes of lobectomy for stage IIIA pN2 NSCLC following induction therapy in 111 patients between 1995 and 2012. Video-assisted thoracoscopic surgery (VATS) use increased during the study period. Between 2008 and 2012, 72% of patients were approached by VATS without any changes in survival patterns [33]. The authors conclude that VATS can be selectively employed in patients with IIIA N2 disease without compromising survival.

## Surgery in the immunotherapy era

Immune therapy, principally with checkpoint inhibition via monoclonal antibodies targeted against PD-1 and PD-L1, has revolutionized the treatment of stage IV NSCLC, with almost all patients now eligible for treatment either as single agent or in combination with chemotherapy [34]. Durvalumab, a PD-L1 antibody, was investigated for treatment of locally advanced NSCLC in the landmark PACIFIC trial, which enrolled patients with unresectable stage IIIA and IIIB NSCLC following completion of concurrent chemoradiotherapy without disease progression. Patients were randomized to durvalumab versus placebo. Initial interim analysis revealed significantly improved PFS (16.8 months versus 5.6 months) with durvalumab as compared to placebo, leading to FDA approval of the drug for patients with unresectable stage III disease who do not progress on chemoradiotherapy [35]. Overall survival was reported in September 2018 and was increased in the durvalumab group as compared to the placebo arm (66.3% versus 55.6% at 2 years, HR for death 0.68) [36]. While ground breaking, it is unclear if the results of

the Pacific trial can be compared head-to-head with other trials for IIIA disease. The trial design was unique in that patients were not randomized at the initiation of therapy, but rather after the completion of chemoradiotherapy; therefore, those who did not tolerate or progressed during the initial line of treatment were not included, selecting for a favorable subset. Additionally, there was no strict definition for "unresectable" disease, and this can vary significantly based on provider expertise and institutional biases.

While outcomes for unresectable disease have historically been worse than for resectable disease, the advent of checkpoint blockade presents an entirely new treatment paradigm for patients with IIIA disease. There are currently multiple ongoing trials evaluating the use of immune therapy in combination with surgery in resectable IIIA disease, most targeting stage II–IIIA patients (Table 2). In data presented at the 2018 American Association of Thoracic Surgeons (AATS) annual meeting, Broderick and colleagues showed that resection can be performed safely in patients with stage IB to IIIA tumors who had received two doses of neoadjuvant nivolumab without surgical delay or increased perioperative morbidity or mortality. Additionally, they demonstrated MPR to therapy (≤ 10% remaining viable tumor cells) in 45% of patients, and mediastinal downstaging in 38% [37••, 38•]. Similarly, short-term surgical results from the initial cohort of resected patients from the Lung Cancer Mutation Consortium (LCMC) trial of perioperative atezolizumab were reported at American Society of Clinical Oncology (ASCO) in 2018 and reported no increased morbidity or mortality and poor correlation

**Table 2. Active and recently proposed trials of neoadjuvant immunotherapy and resection for stage III NSCLC**

| NCT no. | Sponsor | Phase | Stage | Neoadjuvant intervention | $1^{o}$ endpoint | Target accrual |
|---|---|---|---|---|---|---|
| 2998528 | Bristol-Myers Squibb | 3 | IB-IIA | Nivo+Ipi vs. Nivo+Chemo vs. Chemo | MPR | 350 |
| 3158129 | MD Anderson | 2 | I-IIIA | Nivo+Ipi vs. Nivo+Chemo vs. Nivo | MPR | 66 |
| 2259621 | Sydney Kimmel Cancer Center | 2 | IB-IIIA | Nivo+Ipi vs. Nivo | Safety and feasibility | 30 |
| 2927301 | Genetech (LCMC) | 2 | IB-IIIB | Atezo | MPR | 180 |
| 2572843 | SAKK | 2 | IIIA | Duva+Chemo | Event-free survival | 68 |
| 2818920 | Duke Cancer Institute | 2 | IB-IIIA | Pembro | Surgical feasibility | 32 |
| 3237377 | Sydney Kimmel Cancer Center | 2 | IIIA | Durva+XRT vs. Durva+Tremi+XRT | Safety and feasibility | 32 |
| | Alliance | 2 | IIIA/IIIB | Durva+Chemo | MNC | 42 |
| 3425643 | Merck Sharp & Dohme | 3 | IIB-IIIA | Pembro+Chemo vs. Chemo | EVS | 786 |

*Nivo* nivolumab, *Chemo* chemotherapy, *MPR* major pathologic response, *Ipi* ipilimumab, *LCMC* Lung Cancer Mutation Consortium, *Atezo* atezolizumab, *SAKK* Swiss Group for Clinical Cancer Research, *Durva* durvalumab, *EVS* event-free survival, *Pembro* pembrolizumab, *MNC* mediastinal nodal clearance

**Table 3. Short-term outcomes of initial trials of induction immunotherapy for resectable NSCLC**

| Author | Treatment | No. | Year | Stage | RR | MPR | AE > Gr3 | Operative mortality |
|---|---|---|---|---|---|---|---|---|
| Forde/Broderick [37••, 38•] | Nivo+ Surgery+SOC adjuvant | 21 | 2018 | I-IIIA | 10% | 45% | 4% | 0% |
| Rusch [39•] | Atezo+Surgery+SOC adjuvant+Atezo | 37 | 2018 | IB-IIIB | 5% | 19% | 8% | 0% |
| Cascone [40] | Nivo+Surgery | 17 | 2018 | I-IIIA | 19% | 25% | 9% | 4% |
| | Nivo+Ipi+Surgery | 16 | | | | 27% | | |

*RR* radiographic response rate, *MPR* major pathologic response rate, *AE* adverse events, *nivo* nivolumab, *SOC* standard of care, *atezo* atezolizumab, *Ipi* ipilimumab

between radiographic and pathologic response [39•] (Table 3). Trials examining combinations of surgery and immune therapy are actively changing the treatment landscape, and results should be watched closely and with excitement.

## Summary

Locally advanced NSCLC is a heterogeneous disease cohort. As such, successful management requires a wide range of therapies and some nuance to appropriately tailor treatment regimens to suit the individual patient and tumor. The role of surgery in the treatment of stage III NSCLC remains controversial. In general, there is limited data that supports resection for those with IIIB and IIIC disease, outside of highly specialized centers. Surgery has a more significant role in the management of patients with IIIA disease, but numerous aspects of that involvement continue to be debated. The overwhelming majority of patients with resectable, non-bulky N2 nodal involvement should be considered for induction therapy prior to resection. The choice of induction regimen is highly debated, but the current pendulum appears to be swinging away from the inclusion of radiation, as a clear OS benefit has not been demonstrated. In cases in which lobectomy is not feasible and pneumonectomy is required, care should be taken, as perioperative mortality can be significantly increased and referral to thoracic surgeons and high volume centers of excellence should be considered. Those patients with complete pathologic responses to induction who can be resected by lobectomy have the best prognoses, while those with residual N2 disease should be considered for surgery on a case-by-case basis, with the knowledge that prognosis is relatively poor. Patients who progress during induction therapy should generally not undergo resection, although such rules may not apply with use of induction with immune checkpoint inhibitors because pseudo-progression at primary and nodal sites can be seen and radiographic and pathologic responses do not correlate with these agents.

A general consensus has never existed with regard to the role of surgery in the management of patients with locally advanced NSCLC.

Patients, surgeons, and oncologists are finding promising therapeutic developments in immune therapy; however, they are now faced with the integration into already complex treatment algorithms.

## Compliance with Ethical Standards

**Conflict of Interest**
Darren S. Bryan declares that he has no conflict of interest.
Jessica S. Donington has received honoraria and reimbursement for travel expenses from AstraZeneca.

**Human and Animal Rights and Informed Consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

## Publisher's Note



## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance


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