Intraoperative Challenges After Induction Therapy for NSCLC: Impact of Nodal Disease on Technical Complexity

Hope A. Feldman, MD, Nicolas Zhou, DO, Nathanial Deboever, MD, Wayne Hofstetter, MD, Reza Mehran, MD, Ravi Rajaram, MD, David Rice, MD, Jack A. Roth, MD, Boris Sepesi, MD, Stephen Swisher, MD, Ara Vaporciyan, MD, Garrett Walsh, MD, Myrna Godoy, MD, Phd, Chad Strange, MD, Mara B. Antonoff, MD

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**Nodal Findings:**
- cN1 Disease
- Nodal Reduction ≥30% in response to Neoadjuvant therapy

**Are Associated With:**
- Lymph node adherent to pulmonary artery
- Proximal pulmonary artery control required
- Nodal adherence to artery forces change in approach to vasculature
- Arterial sleeve or arterioplasty is required

**Necessitating Adequate:**
- Surgeon expertise
- Anesthesia preparation
- Informed consent
- Blood bank

*To Optimize Patient Safety*

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Intraoperative Challenges After Induction Therapy for NSCLC: Impact of Nodal Disease on Technical Complexity

Hope A. Feldman MD1, Nicolas Zhou DO1, Nathanial Deboever MD1, Wayne Hofstetter MD1, Reza Mehran MD1, Ravi Rajaram MD1, David Rice MD1, Jack A. Roth MD1, Boris Sepesi MD1, Stephen Swisher MD1, Ara Vaporciyan MD1, Garrett Walsh MD1, Myrna Godoy MD, Phd. 2, Chad Strange MD2, Mara B. Antonoff MD1

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GLOSSARY OF ABBREVIATIONS:

CT: computed tomography
EBL: estimated blood loss
NSCLC: non-small cell lung cancer
PA: pulmonary artery
PET: positron emission tomography
cN: clinical node status
CENTRAL PICTURE LEGEND (83/90 char):

Imaging and intraoperative findings reveal lymph node adherence to pulmonary artery

CENTRAL MESSAGE (193/200 char):

When undertaking lung resection after induction therapy, radiographic extent of nodal response to therapy and hilar nodal involvement indicate greater likelihood of needing advanced techniques.

PERSPECTIVE STATEMENT (343/405 char):

Neoadjuvant therapy prior to surgical resection of non-small cell lung cancer has been well-recognized as being associated with greater case complexity. We have identified specific clinical predictors of objective measures of technical complexity. Adequate preparation will allow for the safe completion of these technically challenging cases.
ABSTRACT (250/250):

Objectives: Neoadjuvant therapy has been theorized to increase complexity of non-small cell lung cancer (NSCLC) resections; however, specific factors contributing to intraoperative challenges after induction therapy haven’t been well-described. We aimed to characterize the impact of nodal involvement and nodal treatment response on surgical complexity after neoadjuvant therapy.

Methods: We identified patients treated with neoadjuvant therapy followed by anatomic lung resection for cN+ NSCLC between 2010-2020. Patients were categorized by clinical N1 vs N2 disease. To evaluate impact of nodal response to therapy, thoracic radiologists measured clinically suspicious and pathologically involved lymph nodes pre- and post-induction therapy. Operative reports were reviewed to identify technical challenges specifically related to nodal disease. Categorical outcomes were compared using Fishers exact test.

Results: 124 patients met inclusion criteria, among whom 107 (86.3%) were treated with neoadjuvant chemotherapy, while chemoradiation (n=8) and targeted therapy (n=9) were less common. In cases with N1 disease, 8/38 (21.0%) required proximal pulmonary arterial control, while this was necessary in only 2/88 (2.3%) of N2 cases (p=0.001). Likewise, sleeve resection and arterioplasty were needed more frequently during resection of N1 disease (7/38, 18.4%) vs N2 disease (0/88, p<0.001). Increased nodal response to therapy was associated with greater likelihood of requiring change in vascular approach (p=0.011).

Conclusions: After induction therapy, N1 disease was associated with greater need for complex surgical maneuvers than N2 disease. Likewise, substantial treatment response was associated
with increased intraoperative technical challenges. Recognizing such factors enables surgical teams to engage in appropriate operative planning to ensure patient safety.

KEYWORDS (3-7): non-small cell lung cancer; neoadjuvant therapy; surgery; pulmonary artery; nodal disease
Non-small cell lung cancer (NSCLC) remains the leading cause of cancer related deaths in both
men and women in the US and worldwide.\(^1\) In recent years, substantial developments have been
made in the realm of pharmacologic targets for this disease. Nonetheless, while the agents and
regimens available for NSCLC rapidly evolve, surgery continues to serve as an integral
component of multimodal care for patients with lung cancer. Resection following induction
therapy has been a long-time standard of care for patients with locally advanced disease, and new
indications are on the horizon for neoadjuvant therapy in earlier stage resectable disease.
Induction treatment in the setting of stage IB disease is currently being evaluated in a number of
ongoing clinical trials.\(^2\) Even among patients with oligometastatic stage IV NSCLC, the role for
local consolidative surgery after systemic therapy has been associated with clear survival
benefits.\(^3\)\(^-\)\(^5\) As a result, surgeons are operating on patients with advanced disease who may have
historically been offered systemic therapy only.

Surgical indications for NSCLC patients pre-treated with systemic therapy are expanding
throughout all stages of the disease spectrum. As such, previous investigators have evaluated
pathologic endpoints, survival benefits, and care-plan adherence in association with the receipt of
neoadjuvant therapy, through a number of important recent clinical trials.\(^6\)\(^-\)\(^11\) However, limited
data exist regarding the objective impact of neoadjuvant treatment on operative challenges such
as blood loss, operative time, and surgical approach.\(^12\)\(^-\)\(^16\) Moreover, there is a definite paucity in
the literature pertaining to objective measures of technical complexity in this setting, as well as
the extent to which response to neoadjuvant therapy may contribute to increasing operative
challenges.

There are a number of factors recognized to contribute to the technical complexity of anatomic
lung resection, including but not limited to central tumor location, large tumor size, reoperative
procedures necessitating adhesiolysis, preoperative radiation obliterating the surgical planes, and tumor involvement of adjacent structures such as the superior vena cava or vertebrae. Well-trained surgeons may be equipped with the skills needed to navigate these challenging scenarios, but adequate operative planning is pivotal to performing such procedures safely and ensuring that all necessary personnel and resources are readily available when challenges arise. At this time, little is known regarding potential radiographic or clinical findings that may be likely to be correlated with more complex operative cases, nor is there even clear consensus in terms of defining those elements which may constitute a complex case.

The use of radiologic studies to predict intraoperative complexity has not been rigorously evaluated. Moreover, without concrete, objective measures, inter-rater reliability of interpreting such scans can be particularly suboptimal. This issue was exemplified by prior investigators who showed that the use of chest imaging to merely predict extent of surgical resection was subjectively dependent on the experience of the person reading the scan.\textsuperscript{17} With regard to using preoperative data to predict surgical complexity, clear, objective measures are clearly in need. A limited list of vague findings on preoperative imaging and bronchoscopy have been associated with the intraprocedural presence of adherent lymph nodes\textsuperscript{18}—though data associating these findings with intraoperative events are lacking.

In this study, we aimed to evaluate the impact of nodal response to preoperative therapy on intraoperative complexity of anatomic lung resections performed for NSCLC. We hypothesized that extent of nodal reduction would correlate with intraoperative challenges. Thus, we aimed to assess the relationships between nodal involvement and nodal reduction on subsequent objective, measurable intraoperative events related to surgical complexity.
MATERIALS AND METHODS

Study Population

Prior to retrieval of data, a waiver of informed consent was obtained from our institutional review board (2020-0929 Approved 10/5/2020). A prospectively maintained institutional database was queried to identify patients treated with neoadjuvant therapy followed by anatomic surgical resection for node-positive NSCLC between January 2010-May 2020. To be included in the study, patients were required to have cross-sectional chest imaging [CT and/or positron-emission tomography (PET)/CT] available for review from both pretreatment and preoperative time points. Patients were excluded from primary analyses if they did not have histologic confirmation of nodal involvement, if the treatment was for recurrent disease, or if they were treated with a regimen not currently approved for standard of care neoadjuvant therapy. A comparison cohort was identified consisting of patients who underwent upfront surgical resection for cN1 pN1 disease during the same time period.

Radiologic Evaluations

PET and/or CT scan(s) were reviewed for each patient prior to the initiation of neoadjuvant therapy and also following completion of neoadjuvant treatment. Targeted lymph nodes to be measured were selected based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, and short-axis diameter was measured on both pre- and post-treatment imaging studies. Additionally, all nodes proven to be positive for malignancy based on pathologic assessment were identified and measured. Lymph nodes were defined as pathologically positive based on
pre-treatment biopsy and/or surgical pathology. Among patients for whom CT scans were
obtained without contrast, accurate objective measurement of hilar lymph nodes was limited. In
these cases, the largest pre-treatment lymph node station was evaluated for nodal reduction.
Imaging studies were reviewed by 2 experienced dedicated thoracic diagnostic radiologists (CDS
and MG).

Operative Complexity

Operative reports were reviewed for the presence or absence of the following criteria: lymph
nodes described as matted/sticky/hard; lymph nodes unable to be removed from the pulmonary
artery (PA); lymph node adherence to the (PA) resulting in tear; lymph nodes forcing a change in
approach to vascular dissection; proximal and/or intrapericardial PA control required due to
nodal adherence; change in extent of resection due to lymph nodal adherence to structures; and
pulmonary arterioplasty or sleeve resection related to nodal adherence. Cases where pulmonary
artery reconstruction was required due to central tumor involvement were not counted. A change
in approach to vasculature was defined as a dissection beginning with the artery first and the
surgeon switching to vein first approach or vice versa due to encountering difficulty related to
nodal adherence. These criteria were selected in advance of chart review based on input from 9
experienced thoracic oncologic surgeons as being representative of potential technical findings
encountered and maneuvers performed in response to challenging nodal dissections. Operative
approach was left to surgeon discretion.

Statistical Analyses

Continuous variables were presented as median and interquartile range and categorical variables
were expressed as frequency and percentage. Differences between groups were analyzed using
the Mann-Whitney U test for continuous data and Pearson’s chi-square or Fisher’s exact test for categorical data as appropriate. Based on the findings from these preliminary analyses, as well as important clinicopathologic data determined a priori, multivariable linear regression models were created to evaluate the relationship between variables associated with increased risk of surgical complexity and surgical outcome variables. Models were checked for violation of collinearity. For all analyses, $P<0.05$ was considered statistically significant. All analyses were performed using R, version 4.0.2.

**RESULTS:**

The database query identified 180 patients treated for N+ NSCLC, of whom 124 met inclusion criteria and were therefore included in analyses (Figure 1). Patients were fairly evenly distributed between sexes (63 female, 51%), and the majority presented with clinical stage IIIA disease (75, 60%), adenocarcinoma (79, 64%), and a history of current or prior cigarette smoking (102, 82%) (Table 1). Of 124 surgical procedures performed, 107 (86.3%) were initiated via thoracotomy approach, with 2 of 17 (11.8%) minimally invasive cases converted to open. Of the 17 cases begun via minimally invasive technique, 9 were attempted VATS with two converted non-emergently to open and 8 were begun and completed via RATS. Three-quarters of the resections were performed as lobectomies N=95 (76.6%). The remaining procedures consisted of 9 bilobectomies (7.3%), 14 pneumonectomies (11.3%) 1 segmentectomy (0.8%) and 6 sleeve lobectomies (4.8%). The median percent short-axis reduction in lymph node size was 26.6% (IQR 9.3%-40%), and, thus, a cutoff value of 30% was chosen for subsequent analyses of nodal reduction by rounding to the nearest tenth.
Impact of Nodal Stage on Need for Advanced Operative Maneuvers

We first compared the frequencies of need for advanced technical maneuvers between those patients with cN1 disease versus those with cN2-3 disease. Importantly, we found that those patients with cN1 disease were reliably more likely to require a change in approach to the vascular dissection due to adherent lymph nodes (21.1% vs 7.0%, p=0.035), with more cases necessitating proximal pulmonary artery control (21.1% vs 2.3%, p=0.001) and even intrapericardial pulmonary artery control (p=0.03) to safely perform the vascular dissection. Furthermore, all cases necessitating arterioplasty or arterial sleeve due to adherent lymph nodes occurred in cases performed for patients with cN1 disease (Table 2). A subgroup analysis comparing complexity of cases performed in patients with N1+N2 nodal stations involved versus those with skip N2 disease can be found in supplemental table 1.

Impact of Nodal Response to Therapy on Need for Advanced Operative Maneuvers

We next examined the effect of response to therapy, as indicated by percent short-axis reduction following neoadjuvant therapy, on the frequency of challenging intraoperative nodal findings requiring advanced maneuvers. We found that greater than 30% short-axis nodal reduction was associated with the node being unable to be removed from the PA (15.8% vs 3.0%, p = 0.023) as well as an increased likelihood of requiring a change in approach the vasculature (19.9% vs 4.5%, p = 0.011) (Table 3).

Hilar Nodal Reduction and Surgical Complexity

40 (32.3%) patients had histologically confirmed hilar nodal (levels 10-11) involvement. Among these individuals, 34/40 (85.0%) were evaluated for hilar nodal response to therapy. (Six patients
with hilar nodal disease underwent cross sectional imaging without intravascular contrast, limiting the measurement of hilar nodal stations.) In this subset of the entire cohort, 6 of 18 (33.3%) patients with nodal reduction greater than 30% required a change in approach to vasculature while 2 of 16 (12.5%) with lesser response required a change in approach (Table 4).

While this trend may indicate a signal that merits further investigation, it did not reach statistical significance within the power limitations of this study. Of the 40 patients with histologically confirmed hilar nodal involvement, 13 had nodal involvement on pretreatment biopsy and subsequently had nodal complete response on surgical pathology. 5/13 (38.5%) required arterioplasty due to lymph node adherence to the pulmonary artery, 5/13 (38.5%) required proximal pulmonary artery control and in 5/13 (38.5%) the nodal adherence necessitated a change in response to vasculature.

**Use of Novel therapeutic Agents**

For the purpose of our primary analyses described above, we excluded patients who received therapeutic agents outside of currently approved, standard-of-care therapy. However, given the potential likelihood for future expansion of our pharmacological armamentarium, as well as the great utility of developing a foundation for elucidating the intraoperative findings after receipt of such agents, we conducted additional exploratory analyses of this cohort of individuals. When analyses were performed in this subset of patients (n = 21), our findings were similarly upheld. Specifically, we found that in resections performed in patients with either cN1 disease or nodal reduction greater than 30% (n=14), 7 (50%) included descriptions of lymph nodes that could not be removed from the PA, 6 (42.9%) required arterioplasty related to nodal findings, and 2 (14.2%) necessitated sleeve resection due to adherent nodes. When we reviewed cases without these risk factors in this cohort (n=7), 2 (28%) described nodes that could not be removed from
the PA, 2 (28%) required a change in vascular approach, and 0 cases required sleeve or arterioplasty (sTable2). While these findings were not statistically significant, likely due to a small patient population, they are clinically important differences.

**Perioperative Outcomes**

All 124 cases were completed safely, with a median estimated blood loss (EBL) of 200 (IQR 150-302.5) mL and procedure duration of 194 (IQR 149-236) minutes. The median length of stay was 5 (IQR 3-6) days. In total, 15 (11.2%) patients experienced a complication that would be classified as Clavien-Dindo grade 3 or greater, including 2 patients (1.5%) who died during the index hospitalization. The causes of death were related to pneumonia and myocardial infarction. The most common complication was atrial fibrillation requiring medical management in 15 patients (12.1%), followed by discharge with home oxygen (n=11, 8.9%) and discharge with chest tube (n=10, 8.1%) (Table 5). Neither cN nor reduction greater than 30% was predictive of increased EBL (sTable3) or length of procedure (sTable4). However, when analyzing cN2-3 vs. cN1 independently, we found that the association was negatively correlated with EBL (estimate -112, SE 56.5, p=0.050), indicating that patients with cN1 disease are more likely to have increased EBL.

**Comparison to Cohort Undergoing Upfront Resection**

The database query identified 41 patients with cN1 pN1 disease managed with upfront surgery. When compared to patients who underwent neoadjuvant therapy followed by surgical resection for cN1 disease, those treated with primary resection were less likely to require proximal PA control (4.9% vs 21%, p=0.043), intrapericardial PA control (0 vs 10.5%, p=0.049), or arterioplasty/sleeve due to adherent lymph node (0 vs 18.4%, p=0.004) (sTable5).
DISCUSSION:

In this study, we found that both cN1 disease as well as nodal response to therapy as indicated by percent of short-axis reduction were associated with increased complexity of subsequent anatomic lung resection. Our criterion-centered evaluations of technical complexity are novel, distinctly different from prior studies that relied upon subjective assessments to evaluate operative difficulty, and serve as a foundation for future studies that may use surgical complexity as an endpoint of interest. By defining operative complexity using objective measures, we aim to create a mechanism for reporting difficulty that conveys not only that a case was challenging, but what the source of difficulty was and how it was managed. Further, we have shown that cN1 involvement as well as significant nodal response to therapy are both associated with increased likelihood of requiring advanced maneuvers to complete the vascular dissections. Both of these variables are concrete values that are known before the surgical case and may allow for anticipation of difficulties while enabling adequate planning to ensure safe outcomes (Video).

In recent work published by Takeda et al, the authors found that lymph node size greater than 8 mm detected on CT scan and dark pigmentation on bronchoscopy could be used to stratify patients according to risk of PA-adherent nodes. Further, Li and colleagues found that interference by lymph nodes was the most common reason for conversion from minimally invasive lung resections to open thoracotomy. In our study, we have corroborated these findings and further addressed the same problem using a more specific, objective approach to predicting intraoperative markers of case complexity. We have successfully shown that both
nodal response to therapy and location of involved nodal stations are important predictors of intraoperative challenges. Unlike prior studies, we did not find that this nodal adherence was associated with increased conversion to open thoracotomy, though it is important to note that the majority of these post-induction cases in this series were initiated via open approaches. The current study focused on the hypothesis of nodal reduction in size, as we felt aimed to characterize the specific impact of this sclerotic response on surgical complexity, and, as such, we have not delved into other clinical measures of tumor response, such as reduction of FDG avidity on PET, RECIST criteria, or others. While those other measures may be of interest in predicting pathologic response, they were not related to our central hypothesis of nodal sclerosis impacting technical components of the operation. Moreover, in addition to identifying risk factors for case complexity, this study is one of the first to thoroughly outline intraoperative aspects of case complexity. Building on prior investigations which have described potential intraoperative features of challenging cases, this study has produced a comprehensive list of intraoperative findings for measuring complexity of dissection. These features may be used in future evaluations of surgical complexity, particularly in the growing body of clinical trials aiming to assess pathologic endpoints after neoadjuvant therapy.

There is a shifting paradigm in the management of NSCLC, in that treatments previously found to be effective in the adjuvant setting are now being evaluated in the neoadjuvant setting and among patients with earlier stages of disease. Concurrently, the established role of surgical resection in the management of oligometastatic disease has expanded the patient population for whom surgical may play a role in multimodal therapy. As a result of these changes, the patients whom we are encountering in the operating room are different than those we managed surgically as recently as 5 years ago. Previous authors have described increased complexity associated with the receipt of neoadjuvant therapy. Similarly, operating on patients with advanced and
oligometastatic disease poses unique challenges. However, it is important to note that in this study as well as the prior studies out of our institution, these procedures can be performed safely. Given that these cases were all completed safely and with reasonable morbidity, the question may arise as to the relevance of surgical complexity. It should be clearly recognized that this series represents an institutional series at a large, urban, academic cancer center, with a group of 9 dedicated thoracic surgical oncologists, well-supported by dedicated thoracic anesthesiologists, thoracic nursing and scrub teams, and ample resources to conduct high-level complex operations. However, at a national level, nearly 1 in 10 anatomic lung resections for lung cancer are performed by individuals without training in cardiothoracic surgery, with an estimated 1,500 cases being performed by general surgeons over a recent four-year period. Surgical outcomes have been demonstrated to be better among patients treated by thoracic surgeons and at high-volume centers, yet we must recognize the ongoing receipt of NSCLC surgical care in a variety of environments, by surgeons with training in general surgery, cardiovascular surgery, and thoracic oncology. While the complication rate in our cohort is appropriate for the procedures performed, it should be noted that this was achieved at a high-volume institution, and even still, in 4 cases, a second thoracic surgeon was required to assist in the operating room due to complexity of the cases. Moreover, it is imperative to recognize that surgeon skill alone does not result in case success; rather, it is the combined efforts of a well-prepared team including anesthesia, nursing, blood bank, sterile supplies, and more. Appropriate rooms and equipment must be available, adequate time must be allocated, and accurate expectations must be presented during the informed consent process. All of these elements are necessary to promote safe outcomes following these surgical resections.
An additional important consideration raised by the evolving surgical cohort is the need to expose trainees to more technically challenging operative cases. It may be more common for faculty surgeons to take over during more challenging cases, and, at times, this is necessary to promote a safe environment for the patient. However, it must be recognized that every operating room encounter may serve as a valuable educational tool for a trainee, and appropriate preoperative planning discussions and debriefing are key components to such educational experiences. Using these tools, even portions of the resection performed by the attending surgeon may effectively demonstrate how to manage friable tissue, incomplete planes, and, very importantly, how to work collaboratively on a team to ensure safe patient outcomes.

Additionally, with an increasing level of operative of surgical complexity, the value of simulation and practice outside of the operating room cannot be overstated. While this is the first paper to show that clinical nodal staging and response to therapy may be correlated with increased risk of operative complexity, there are some inherent limitations. First, this is a retrospective analysis that relied on review of operative reports, and, thus, the validity of the analyses required detailed description of the procedure by the provider. Fortunately, all 124 patients included in the analysis had operative reports that provided detailed description of the dissection of the hilum, and any questions of findings were reviewed by a second surgeon-investigator. Additionally, the number of patients included in the analysis, as well as the infrequency of operative complexities limited the power and types of feasible analyses that could be performed. Our aim was to show trends in correlation, and the sample size was sufficient for to demonstrate a meaningful relationship between clinical findings and operative complexity. Furthermore, a comparison was made between patients undergoing upfront resection versus those who receive neoadjuvant therapy and there are likely variables not accounted for in the
analysis that may contribute to different operative findings in these two populations. As this
study utilizes data collected from a single quaternary academic center where, in our practice, we
undertake advanced procedures in sometimes very aggressive disease, there may be limitations
regarding the generalizability of our findings. It will be important moving forward to evaluate
predictors of operative complexity in a variety of settings.

In this study, we have shown that cN1 disease and nodal reduction in short axis diameter of 30%
or greater are associated with increased complexity of anatomic lung resection due to nodal
adherence to the PA. By enabling providers to use these clinical variables to anticipate a more
complex procedure, these findings will allow for improved preoperative planning and acquisition
of appropriate resources to ensure a safe procedure. It is our hope that these clinical variables, as
well as those previously known to contribute to complexity (central tumor location, neoadjuvant
therapy, reoperation, tumor size, involvement of vital structures), will be disclosed in future
clinical studies so as to allow providers to understand potential source(s) of operative complexity
and to anticipate strategies and resources needed for safe and successful management (Figure 2).
REFERENCES:


Legends

Figure 1. Patient flow diagram

Figure 2. Graphical Abstract

Video. Authors presentation of data and discussion of clinical importance
Table 1. Patient Demographics and Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>n=124</th>
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</thead>
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<tr>
<td>Age (years)</td>
<td>62 (56,67)</td>
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<tr>
<td>Sex (female)</td>
<td>63 (51)</td>
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<tr>
<td>Clinical Stage</td>
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<tr>
<td>IIA</td>
<td>8 (6.5)</td>
</tr>
<tr>
<td>IIB</td>
<td>25 (20)</td>
</tr>
<tr>
<td>IIIA</td>
<td>75 (60)</td>
</tr>
<tr>
<td>IIIB</td>
<td>8 (6.5)</td>
</tr>
<tr>
<td>IV</td>
<td>8 (6.5)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>79 (64)</td>
</tr>
<tr>
<td>Squamous</td>
<td>35 (28)</td>
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<tr>
<td>Adenosquamous</td>
<td>2 (1.6)</td>
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<tr>
<td>Neuroendocrine</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>1 (0.8)</td>
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<tr>
<td>Large cell</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (0.8)</td>
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<tr>
<td>NSCLC NOS</td>
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<tr>
<td>Smoking History</td>
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<tr>
<td>Never</td>
<td>22 (18)</td>
</tr>
<tr>
<td>Former</td>
<td>86 (69)</td>
</tr>
<tr>
<td>Current</td>
<td>16 (13)</td>
</tr>
<tr>
<td>Neoadjuvant Therapy</td>
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<tr>
<td>Chemotherapy</td>
<td>107 (86.3)</td>
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<tr>
<td>Chemoradiation</td>
<td>8 (6.4)</td>
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<tr>
<td>Chemo+Targeted*</td>
<td>9 (7.3)</td>
</tr>
</tbody>
</table>

Values represented as N(%) or median (IQR).

*Targeted therapies included Bevacizumab (3), Erlotinib (3), Afatinib (1), Alectinib (1) and Osimertinib(1)

Table 2. Clinical Nodal Status and Intraoperative Challenges

<table>
<thead>
<tr>
<th></th>
<th>cN1 (38)</th>
<th>cN2-3 (86)</th>
<th>p</th>
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<tbody>
<tr>
<td>Node unable to be removed from PA</td>
<td>6 (15.8)</td>
<td>5 (5.8)</td>
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<tr>
<td>Node stuck to PA causing tear</td>
<td>1 (2.6)</td>
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<td>0.307</td>
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Table 3. Clinical Nodal Reduction and Intraoperative Challenges

<table>
<thead>
<tr>
<th>Node reduction &lt;30%, (N=67)</th>
<th>Node reduction 30+%, (N=57)</th>
<th>p</th>
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<tr>
<td>Node unable to be removed from PA</td>
<td>2 (3.0)</td>
<td>9 (15.8)</td>
</tr>
<tr>
<td>Node stuck to PA causing tear</td>
<td>1 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Node forces change in approach to vasculature</td>
<td>3 (4.5)</td>
<td>11 (19.9)</td>
</tr>
<tr>
<td>Intrapericardial PA control due to node</td>
<td>1 (1.5)</td>
<td>4 (7.0)</td>
</tr>
<tr>
<td>Proximal PA control due to lymph node</td>
<td>4 (6.0)</td>
<td>6 (10.5)</td>
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<tr>
<td>Extent of surgery changed due to node</td>
<td>3 (4.5)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Arterioplasty/sleeve due to lymph node</td>
<td>2 (3.0)</td>
<td>5 (8.8)</td>
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</table>

Table 4. Extent of Hilar Nodal Reduction Among Pathologically Involved, Radiographically Measurable Hilar Nodes and Intraoperative Challenges

<table>
<thead>
<tr>
<th>Reduction &lt;30% (N=16)</th>
<th>Reduction 30+% (N=18)</th>
<th>n(%)</th>
<th>n(%)</th>
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<td>Node unable to be removed from PA</td>
<td>3 (18.8)</td>
<td>4 (22.2)</td>
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<tr>
<td>Node stuck to PA causing tear</td>
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<td>1 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Node forces change in approach to vasculature</td>
<td>2 (12.5)</td>
<td>6 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Intrapericardial PA control due to node</td>
<td>1 (6.3)</td>
<td>1 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Proximal PA control due to lymph node</td>
<td>3 (18.8)</td>
<td>4 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Extent of surgery changed due to node</td>
<td>3 (18.8)</td>
<td>1 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Arterioplasty/sleeve due to lymph node</td>
<td>2 (12.5)</td>
<td>3 (16.7)</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Perioperative outcomes

<table>
<thead>
<tr>
<th>Procedure Duration (min)</th>
<th>Median or N (out of 124)</th>
<th>IQR or %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>194</td>
<td>(149,236)</td>
</tr>
<tr>
<td>Length of Stay (Days)</td>
<td>5</td>
<td>(3,6)</td>
</tr>
<tr>
<td>Event</td>
<td>Count</td>
<td>Rate</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>EBL (mL)</td>
<td>200</td>
<td>(150,302.5)</td>
</tr>
<tr>
<td>Clavien Dindo 3+</td>
<td>15</td>
<td>12.1</td>
</tr>
<tr>
<td>Death prior to discharge</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Admission to ICU</td>
<td>4</td>
<td>3.2</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged air leak</td>
<td>8</td>
<td>6.5</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Atelectasis requiring bronchoscopy</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Effusion requiring drainage</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Reintubation</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Respiratory failure and tracheostomy</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>DC with chest tube</td>
<td>10</td>
<td>8.0</td>
</tr>
<tr>
<td>DC with home O2</td>
<td>11</td>
<td>8.9</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afib</td>
<td>15</td>
<td>12.1</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Hematologic transfusion</td>
<td>5</td>
<td>4.0</td>
</tr>
</tbody>
</table>
180 patients with N+ disease treated with neoadjuvant therapy followed by surgery

- 35 patients not meeting inclusion criteria
  - Missing histologic confirmation of nodal involvement
  - Non-anatomic lung resection
  - Treated for recurrence
  - Incomplete treatment records

- 21 patients treated on clinical trial with non-standard of care agent

114 patients included in analysis
Intraoperative Challenges After Induction Therapy for NSCLC: Impact of Nodal Disease on Technical Complexity

**Nodal Findings:**
- cN1 Disease
- Nodal Reduction ≥30% in response to Neoadjuvant therapy

**Are Associated With:**
- Lymph node adherent to pulmonary artery
- Proximal pulmonary artery control required
- Nodal adherence to artery forces change in approach to vasculature
- Arterial sleeve or arterioplasty is required

**Necessitating Adequate:**
- Surgeon expertise
- Anesthesia preparation
- Informed consent
- Blood bank

*To Optimize Patient Safety*

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Limitations

- Single-center retrospective study
- Evaluation of events relied on details provided in operative reports
- Infrequency of operative complexities limits the power and types of feasible analyses
Discussion will be opened by Lana Schumacher from the Mass General Hospital.

Dr. Lana Schumacher (Boston, MA):

Hi. Excellent presentation and thank you for your work. Thank you to the organization and the WTS for allowing me to discuss this, and I appreciate the fact that you did give me the paper to review. And I think you did an excellent presentation. And this is a novel study looking at there are plenty of literature that we've seen with nodal complications leading to bleeding and how to deal with them and whatnot and what to predict. But this is a really nice study where you actually measured measurements of neoadjuvant therapy and the reduction in node response and how this can lead to increased adherence. I know there was a paper that was recently presented or published by [inaudible] that just looked at factors that contribute to nodal adherence but not in this degree, where you're actually looking at what did the neoadjuvant treatment regimen do to your nodes and how is this going to impact you? So, my first question is how do you think your group is going to use this data? Is it going to allow your group to look at the nodal responses measured by a radiologist and say, "Well, maybe I can do this in a minimally invasive fashion," as I noted that about 86% were done open. So, is it going to change the paradigm in how the surgeons look at this?

Dr. Hope Feldman (Houston, TX):

So, thank you for the wonderful question, Dr. Schumacher, and I appreciate that you took the time to review the paper and send me such thoughtful comments. So first, I'd just like to say we don't aim to tell surgeons how to do the cases. Our goal was not to make a comment on the safety of doing these cases open versus minimally invasive. As you could tell, there was a high rate of open surgery among a group of surgeons that are rather facile at minimally invasive procedures. And we would like to reference [inaudible] 2018 paper that noted a minimal difference in outcomes in patients who undergo open versus VATS resections. I think the goal of our paper is to talk about operative planning and resource utilization. So, MD Anderson is fortunate to be an institution where they have dedicated teams. There're nine thoracic surgeons available and in several of these cases, a second thoracic surgeon was required to assist in a more challenging dissection. And so, our goal is to promote safe outcomes for
patients. And as the neoadjuvant regimen evolves, we hope that it can help community physicians begin to plan accordingly so that patients can undergo these more challenging dissections safely,

Dr. Schumacher:

Right. Right. I think that these are very valid points. I know that I mentioned that to you. How can we get this information out to the community? Should this be more standard? Should we be asking our radiologists to actually measure the nodal response more frequently and not just be looking at RECIST criteria? So, I think that-- can you replicate this in the community, do you think, this type of study? Or you have plans for that?

Dr. Feldman:

I think it will be really important to validate the findings of our study. And also, especially to look at the outcomes of these more-- what we would anticipate being more challenging dissections in the community setting to evaluate in a setting that has different resources. Are they seeing the same types of outcomes with regard to complications? Is it safe to still do these procedures? And if so, what resources are going to be needed so that they can plan accordingly?

Dr. Schumacher:

Excellent. My last question, are you going to also look at this study with [newer?] agents? I know you had mentioned that, and hopefully, you will continue this.

Dr. Feldman:

Yes. Dr. Antonov is definitely continuing this work in the setting of targeted therapies and [inaudible].

Dr. Schumacher:

Great. Excellent job.

Dr. Feldman:

Thank you.
Dr. Schumacher:

Thank you.

Unidentified Speaker 2:

You have such a unique opportunity to teach so many people in this room. And you have a slide that says, "Nodal adherence to artery forces change in approach to vasculature." No, it doesn't. It's changing approach to the bronchus. Cut the bronchus. If you just cut the bronchus, you don't have to get around the artery. So, I think that's the big trick. That's why we do - and I know you're not going to believe me, but enough people in the room have seen this - 100% of these robotically. Every single one is done robotically, with a conversion rate of under 2%. And it is better for the patient. So, it's good to say outcomes are the same, but they're not. You'd much rather have those minimally invasive than an open. And we do them together as a team. But I think the unique opportunity here is to teach people when you can't get around an artery, instead of digging around to get-- yes, you get proximal control, but just take a bipolar, if you use a robot. You can lower the FiO2 in the inspired air from the anesthesiologist, but you don't have to. Airway fires don't happen. But if you're worried about it, do it. And just cut the B2 or the B3 or the B1 bronchus. They're usually left upper lobes, almost all of these. If you cut the B2 and then start bringing it back down even to the B4 or 5, the artery's just hanging out in the breeze. And then you can go get it.

Dr. Feldman:

I appreciate that comment. I'm a second-year general surgery resident. Okay. [crosstalk]. [applause]

Dr. Feldman:

[And there's the reason?], so—
Never mind.

Unidentified Speaker 1:

But I'll take--

Dr. Feldman:

So, I'll use that as a learning opportunity. Thank you.
Unidentified Speaker 1:

Wait. Robert, if you still love the node invading the artery, you got to give us leave.

Unidentified Speaker 2:

[inaudible].

Unidentified Speaker 1:

Just to clarify, if you change the order of the steps that you're doing in the operation, that is technically a change in the approach to the vasculature. You're not taking the artery at the time when you otherwise might have done it. You're taking the bronchus first and then approaching the artery from a different angle.

Dr. Feldman:

Thank you.

Unidentified Speaker 1:

Excellent job. [applause]